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Studies on the Spread of Excitation through the Ventricular Myocardium

II. The Ventricular Septum

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The spread of the excitatory process in the ventricular septum of the dog's heart has been studied in the isolated organ perfused by the Langendorff technic. It has been possible to remove large portions of the free wall of the right and left ventricles and explore the septal surfaces under direct vision. The mean excitatory pathway in the muscular mass of the dog's ventricular septum has been demonstrated to be from apex to base. The left side of the septum is activated before the right side, and the apical part of the right side is activated before its base.

WE HAVE previously reported that the spread of the excitatory process in the left ventricular wall appeared to be related to the predominant direction of the muscle fibers.[1] The present report pertains to the excitation of the ventricular septum studied in the isolated perfused organ. It has been found that the mean axis of excitatory potentials of this preparation was such that the base was positive to the apical portion throughout most of the excitation. Preliminary reports on the time of arrival of the excitation on either side of the septum from directly applied electrodes[2] and the vectorgrams[3] of the isolated septum have been presented. While the present work was in progress, Sodi-Pallares and coworkers,[4] using other technics in the intact animal, published investigations leading them to similar conclusions.

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Methods

The isolated dog's heart was perfused by the Langendorff technic, the perfusate being Tyrode's solution to which was added glucose to 1 per cent concentration and small amounts of washed red cells, approximated at 25 to 50 cc. of packed cells per liter. After the heart beat had become stabilized, the free walls of right and left ventricles were removed, exposing the septum to direct exploration. A ridge of the ventricular muscle was left along the A-V (atrioventricular) sulcus so that in effect the "removal" of the free walls could be described as the making of very large windows into the ventricles.

In the early experiments the electrocardiograms were recorded on a Sanborn Tribeam electrocardiograph; in the later experiments, on a Sanborn "Polyviso," to two channels of which was attached a cathode ray oscilloscope (Dumont 304H) so that a vectorgram also could be recorded directly. Time intervals were recorded by the incorporation of an intensity modulator (Hewlett Packard 200B) which gave records that varied in intensity at a 1 millisecond cycle. Photographs were taken of the oscilloscopic screen when desired, with the direct-writing electrocardiograph showing the nature of the mechanism of the beat.

The unipolar electrodes were constructed of saline-soaked cotton in the end of small plastic tubes into which copper wire was entwined. The bipolar electrodes were made from fine enameled copper wires brought through a fine plastic tube, bent over the

end, tied and the enamel broken with a file, the base areas of two wires of the proximity bipolar electrode being 1 mm. apart. The reference electrocardiogram was made with the one wire electrode around the great vessels, the other in the perfusate bath approximately 12 cm. from the heart, which was immersed to about half its length in the perfusate. An upward deflection in this reference tracing indicated relative positivity of the base of the heart to the apex. The tracings designated as "unipolar" were the recorded potentials between an electrode placed directly on the heart and a "distant" electrode placed in the perfusate bath approximately 12 cm. from the heart. In some experiments, the right or left side of the septum was incised under direct vision in those areas where the specialized right and left bundle branches have been alleged or assumed to lie, such incisions being made as a rule 2 to 3 mm. deep, 1 to 2 cm. long and approximately 5 to 10 mm. caudad from the top of the septum.

When the vectorgrams of the specimen were being recorded, a larger deeper container, 20 cm. in diameter and 25 cm. in height, surrounded the heart so that it was completely immersed. Six electrodes were fastened in the container so that the potentials between any two pairs of electrodes could be recorded, and vectorgrams in each of the three planes could be obtained.

Results

Direct Exploration of the Septum. The present observations were made on 15 preparations which represented approximately two thirds of the attempted experiments. In the others the early appearance of ventricular fibrillation, complete heart block or persistent nodal rhythm rendered the preparation unsatisfactory. In the presence of normal sinus rhythm the following findings were uniformly noted.

With removal of the greater part of the free walls of the right and left ventricles, the QRS complex of the reference electrocardiogram without exception changed from a Qr deflection to a practically monophasic R deflection, without any shortening and, as a rule, any lengthening of the duration of the complex. Thus the mean excitatory pathway in the septum was interpreted as oriented from apex to base, with the former being relatively negative to the latter. When the two sides of the septum were tapped to give a bipolar electrocardiogram recording the potential difference between the two sides, multiphasic deflections were obtained frequently, but predominantly the deflection was such as to indicate relative negativity of the left side.

In two experiments a proximity bipolar electrode was pulled through the septum and there was a progressive increase in the delay of activation potential, measured from the onset of the reference QRS, as the electrode passed from the left to the right side.

The onset of the excitatory process as measured by proximity electrodes was earliest at the left side of the septum near the apex. It was also uniformly very early on the right side near the apex. Much less uniform results were obtained from the surfaces of the upper part of the septum both in regard to retests in the same preparation and in different preparations. With one exception the left upper surface of the septum was, by the technics used, excited nearly simultaneously with the lower part. In the exception noted the upper left side of the septum was excited later, that is, 0.025 second after the onset of the reference QRS. The times of excitation of the upper right side of the septum were late in comparison to the other readings, usually occurring about 0.034 second after the onset of the reference QRS (fig. 1). In one preparation (table 1) where the QRS was abnormally long (0.06 second) the onset of the excitatory process on the right side of the septum was unusually delayed—0.055 second in its upper part and 0.040 second in its lower part.

Vectorcardiograms. The vectorcardiograms of the isolated heart, taken in the frontal and sagittal planes, were roughly triple loops consisting first of a negatively oriented loop (which reached its apex in approximately 6 milliseconds), followed by a positively oriented loop and then by a third loop somewhat superimposed on the first (fig. 2). The maximal potentials from the electrical field at the 10 cm. radial distances were of the order of 0.2 mv. In the frontal and sagittal vectorcardiograms shown on the cube in figure 2 it is seen that the initial orientation is such that the bottom of the chamber is relatively positive to the top.

Following removal of the two free walls of the ventricles the vectorcardiogram is uniquely changed and simplified, with the base of the

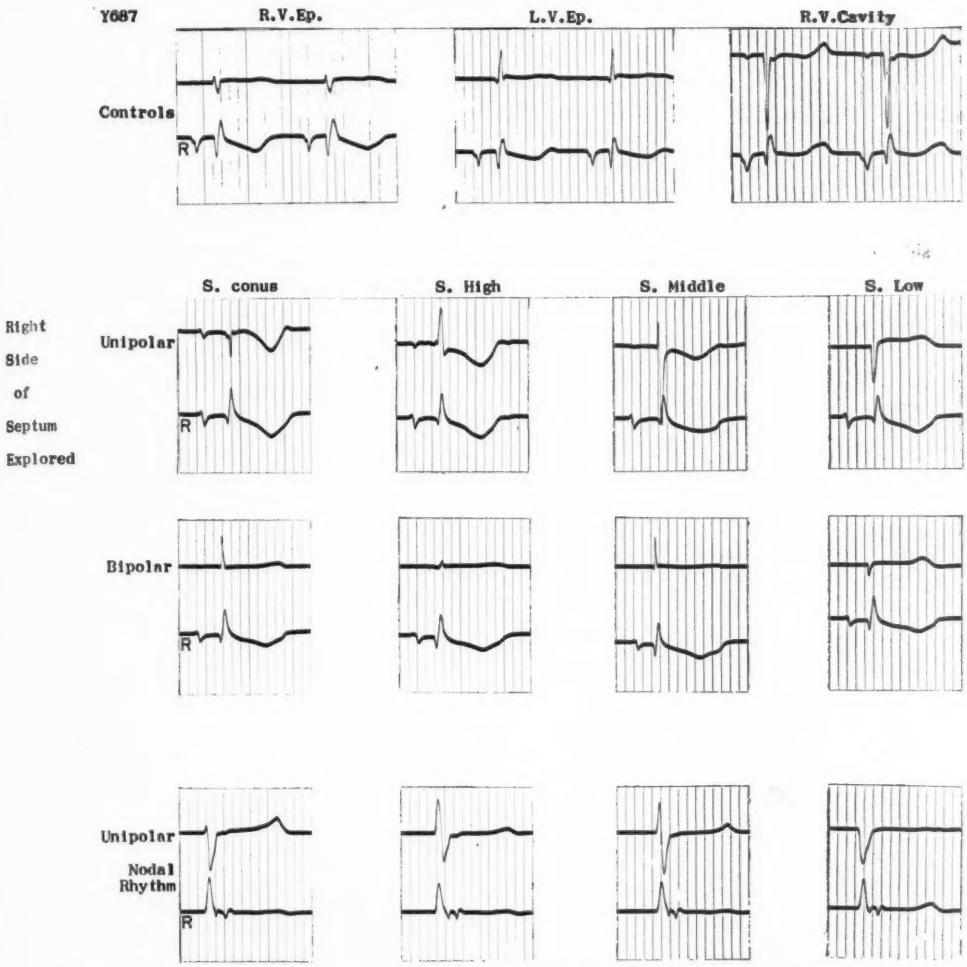

FIG. 1. Records obtained from the isolated perfused heart before and after removal of the free wall of the right ventricle. The lower tracing, R, in each record is the standard reference bipolar electrocardiogram. In the upper control group are the unipolar records obtained respectively from the right ventricular epicardium (R.V.Ep.), left ventricular epicardium (L.V.Ep.) and right ventricular cavity (R.V.Cavity). In the second and third horizontal groups of tracings are the records obtained by direct exploration of the septum by the unipolar and proximity bipolar technics. R indicates the reference tracing, and the tracings from the septum, S, are from the conus area, high on the septum, the mid and apical portions of the septum. In the lowermost horizontal group of records are the potentials recorded from the various portions of the right side of the septum during a period when the heart beat originated in an area other than the sinus, so that an R-P type of "nodal rhythm" resulted. There is a basic similarity between these last records and those obtained with sinus rhythm.

chamber now negative to the top throughout most of the QRS inscription. This is evident in the records taken both in the frontal (fig. 3) and sagittal planes (fig. 4). Records taken in the horizontal plane (fig. 5) are more difficult to interpret, but indicate the orientation of the mean potential so that the left side is predominantly negative to the right. An incidental finding of unusual interest was the recorded vectorgram during a period of

TABLE 1.—*Both Free Walls Removed. Time, in Seconds, of Deflection Recorded from Proximity Electrodes from Onset of QRS in Reference Tracing**

Rate	P-R	QRS	Right side of septum		Left side of septum		Epicardium	
			High	Low	High	Low	Anterior	Posterior
66	0.13	0.06	0.055	0.040				
66	0.13	0.06			0.005	0.000		
66	0.13	0.06					0.032	0.030
Left side of septum cut								
56	0.18	0.09			0.065	0.060		
56	0.18	0.09					0.040	0.045
Right side of septum cut								
62	0.20	0.10	0.060	0.040				
Left cut extended—complete heart block								

* The relative delay in excitation of the right side of the septum in this preparation and a QRS duration of 0.06 second from the onset are to be noted. The excitation arrival on the anterior epicardium (0.032 second) is later by approximately 0.015 second than usually observed; the heart rate is slow and it may be questioned whether the preparation was physiologically in good condition. Notwithstanding such a possibility, the sequence of events following incision into the left side of the septum is instructive.

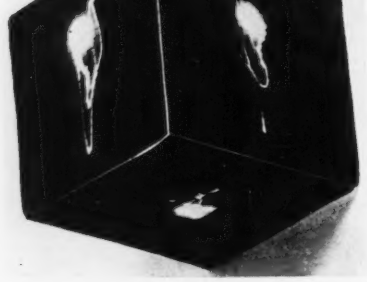

FIG. 2. Vectorcardiograms obtained in three planes of the totally immersed, isolated heart perfused by the Langendorff technic. The records were mounted to form three sides of a cube and rephotographed. The horizontal vectorcardiogram to be correctly representative would have to be mounted in the midst of the cube rather than at the bottom. The main or second loop is spatially oriented in the right anterior quadrant. The beginnings of the tracings in the vertical vectorcardiograms are the thinner downward lines and the ends the thicker wavy lines. The timing signal was not incorporated into the registration of these particular records.

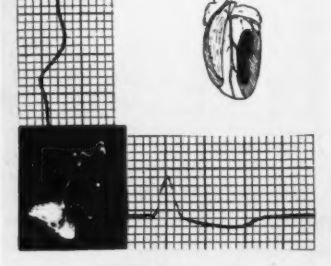

FIG. 3. Vectorgrams of the potentials of the perfused septum in the frontal plane showing the loop oriented in the right upper quadrant of the screen. The beginning of the loop is nearly directly upward, the returning portion is to the right of it. The lower round blob is representative of the maintained injury potential during systole. It is apparent that the vector is oriented so that the apex is negative to the base during the excitatory process. In the sketch, the black area represents the left ventricular "cavity" and the diagonally shaded areas, the ventricular wall. The vertically placed standard-type electrocardiographic tracing shows the potentials between the sides of the chamber (horizontal axis of the vectorgram) and the horizontally placed tracing the potentials between the top and bottom of the chamber (vertical axis of the vectorgram).

idioventricular rhythm, where the loop has reversed its main axis and the excitatory spread is downward from base to apex (fig. 6).

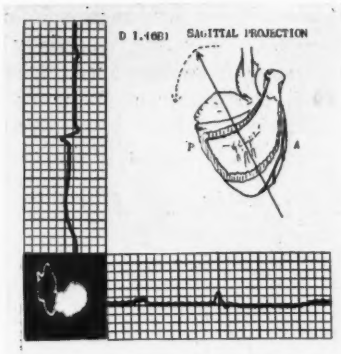

FIG. 4. Vectorgrams of the potentials produced by the isolated perfused septum in the sagittal plane. A, anterior; P, posterior. In the standard tracings, 10 divisions of the voltage scale = 1 mv., and 10 divisions of the time scale = 0.20 second (for example, the P-R interval = 0.20 second). In the cathode ray oscilloscope, positivity of the electrode above the heart relative to the one below the heart caused an upward deflection of the beam, and positivity of the electrode anterior to the heart relative to the one posterior to the heart caused a deflection of the beam to the right.

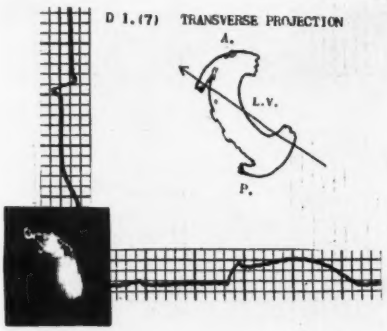

FIG. 5. Vectorgrams produced by the potentials of the perfused septum in the horizontal projection, the tracings being obtained from the anterior-posterior pair of electrodes and the right and left electrodes. The deflections in the early part of the QRS are the important features of the study. The injury effect may be noted with the elevation of the S-T segment in the superior-inferior direction, depression in the right-left direction and the persistent "blob" on the cathode oscilloscopic record on the returning limb of the loop above and to the left of the rest point.

Records Obtained after Cutting the Septum. It was observed that incisions across the right side of the septum, calculated to produce bundle-branch block, caused a delay in the excitatory process reaching the surface above the cut in the area under the tricuspid leaflet and conus area but a less marked effect on the onset of excitation reaching the right side of the septum at the apex (figs. 7 and 8).

Incisions across the left surface of the septum produced uniform results in six experiments with an increase in QRS duration of approximately 0.02 second and a delay in the onset of the excitatory process both above and below the cut (tables 2, 3, 4 and fig. 9). The early onset of excitation on the right side near the apex persisted. The nature of the incisions made in the septum under direct vision is illustrated in figure 10.

When the left side of the septum had been incised, the preparation was most subject to complete heart block when the right side of the septum was incised, and when this occurred it was usually permanent. In one preparation with bilateral septal incisions an unusual event occurred, with normal sinus

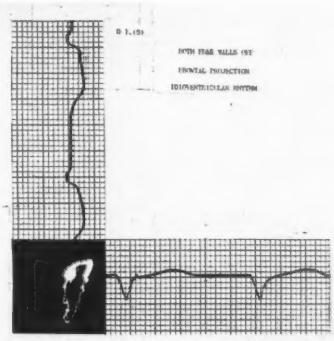

FIG. 6. Vectorgrams of potentials of the perfused septum during idioventricular rhythm. The entirely different orientation of the loop is evident with the vector so oriented that the apex is positive to the base which is interpreted as indicating the reversal of the direction of excitation compared with that occurring in normal sinus rhythm and atrioventricular conduction. The initial part of the loop descends vertically and the following part passes upward on its right. The denser portion of the loop in the right upper quadrant of the oscilloscopic screen represents the injury potential. The QRS was measured as 0.07 second in duration.

rhythm being re-established but with reference QRS reversed in its main deflection (fig. 11). The P-R interval markedly increased. The earliest part of the heart excited appeared to be the left upper side of the septum. In this instance in which both sides of the upper part

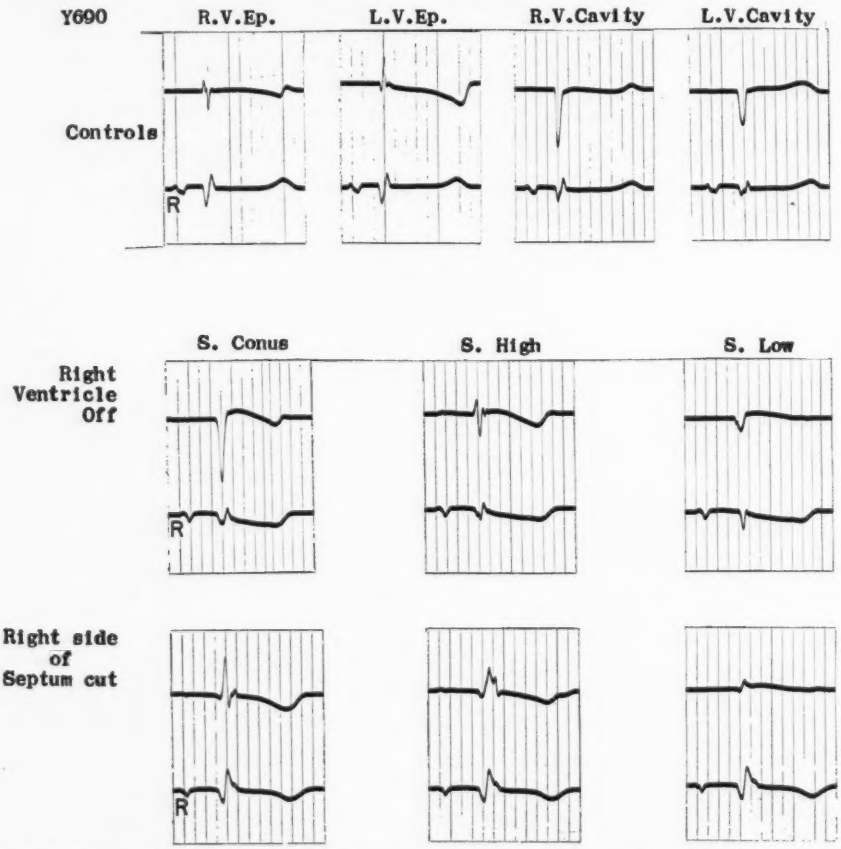

FIG. 7. Tracings taken from a preparation with experimental cutting of the right side of the septum. The exploratory unipolar electrocardiograms are above the reference tracings, R. The induced delay in the excitation, as judged from the predominant negative (intrinsic) deflection, over the upper surface of the septum, above the cut, is to be noted. The abbreviations are explained in the legend for figure 1.

of the septum had been damaged, the excitatory process was apparently spreading downward in the septum, the reverse of the normal mean excitatory pathway.

COMMENT

The observed peculiarities in the manner of the excitation of the ventricular septum in the dog are not without confirmation from other investigators. Using technics essentially similar to the one we have employed, Schneiders[5] investigated the sequence of the excitation process in the isolated heart of the cat and dog. He interpreted his results as indicating an apex-to-base spread of the activation, and the particular point of interest in his experiments relative to ours was the early excitation of the base of the right papillary muscles. In the one pertinent illustration the apex of the heart was excited 0.053 second after the papillary muscle. Apparently he did not investigate the upper part of the right side of the septum nor open

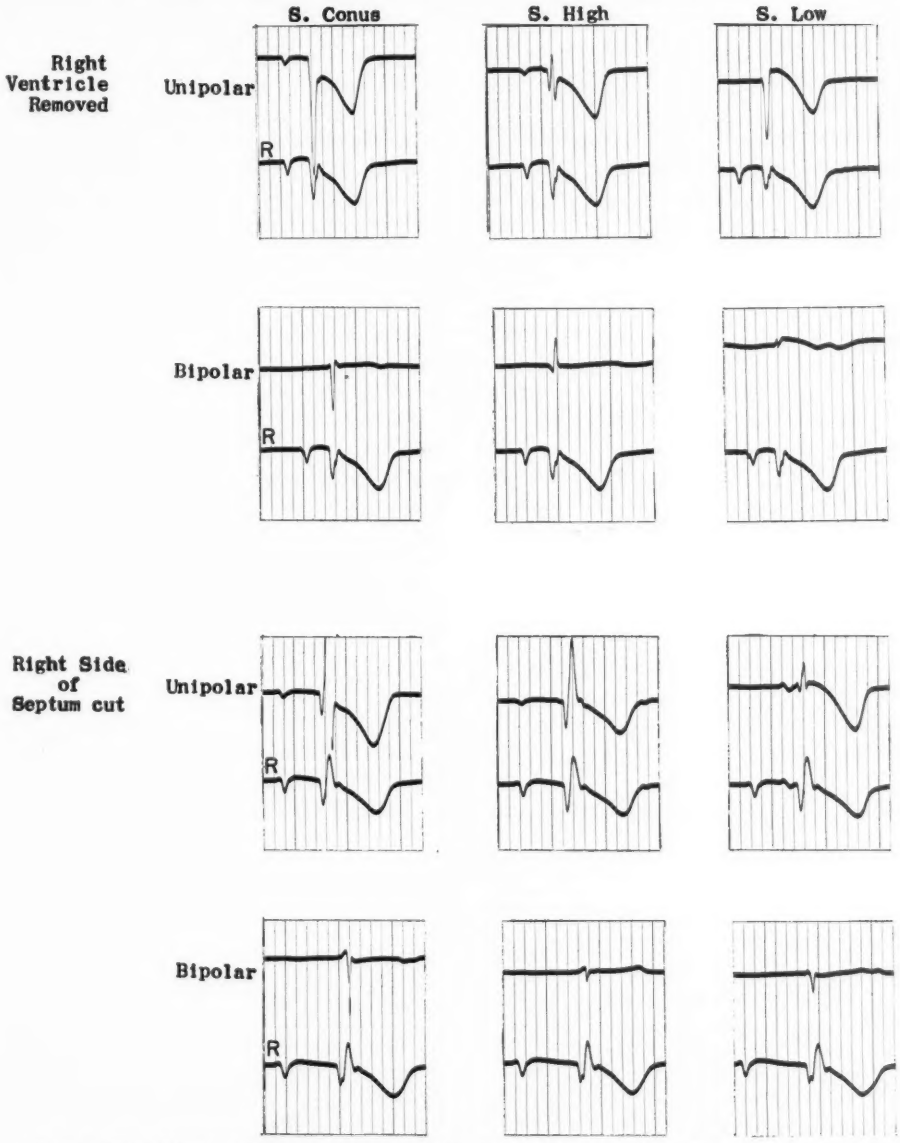

FIG. 8. The abbreviations are explained in the legend for figure 1. The reference tracing, R, is below and the exploratory tracing is above in each record. Following an incision across the upper right surface of the septum the change in the form of the "unipolar" potentials from the upper part of the septum and the evidence of the delay in excitation from both the unipolar and proximity bipolar records are to be noted. In the preparation there was a progressive increase of P-R interval in the latter part of the recording which is believed incidental to the main findings. The change in form in the reference QRS is more marked than appeared in other similar experiments.

the left ventricle to explore the left side of the septum. Lewis and Rothschild[6] reported that the right upper surface of the septum was activated late in comparision to the lower part and attributed this delay to a sparseness or lack of Purkinje fibers in this area. While the

TABLE 2.—*Both Free Walls Removed. Time, in Seconds, of Proximity Bipolar Deflection Related to Reference Tracing*

Rate	P-R	QRS	Right side of septum			Left side of septum	
			Conus	High	Low	High	Low
100	0.10	0.04	0.015				
100	0.10	0.04		0.035			
100	0.10	0.04			0.015		
100	0.12	0.04				0.000	
100	0.12	0.04					0.003
Left side of septum cut							
100	0.15	0.06				0.030	
100	0.15	0.06					0.045
100	0.15	0.06	0.020				
100	0.15	0.06		0.020			
100	0.15	0.06			0.000		
Right side of septum cut—complete heart block							

of a nearly perpendicular spread of the excitation proceeding equally from either side has been generally accepted.

In the intact heart of the dog, Sodi-Pallares and co-workers[4] have been able to explore the septal walls by special electrodes and from the records have adduced that the excitation is earlier in the apical region of the septum than at the base. As collateral evidence they offered the records obtained when ventricular extrasystoles were originated at the apex of either ventricle, with the excitation entering the septum from below, coinciding with the general direction of the activation of the whole heart in heart beats of sinus origin. While their investigations were generally interpreted within the framework of the conventional viewpoints of the right and left bundle systems, it was emphasized that a considerable portion of the septal

TABLE 3.—*Both Free Walls Removed. Time, in Seconds, of Deflection Recorded from Proximity (Contiguous) Electrodes from Onset of QRS in Reference Tracing*

	Rate	P-R	QRS	Right side of septum			Left side of septum	
				Conus	High	Low*	High	Low
Control isolated heart	80	0.12	0.05					
Right ventricle off	78	0.12	0.09	0.018		0.013		
	78	0.12	0.09		0.040	0.010		
Left ventricle off	66	0.13	0.08				0.000	0.000
	66	0.13	0.08		0.050		0.005	
	66	0.13	0.08			0.005		0.000
Left side of septum cut	68	0.14	0.07			0.000		0.042
	68	0.14	0.07				0.050	0.042
Cut extended	68	0.14	0.07				0.040	0.040
	68	0.14	0.07		0.040	0.000		
Right side of septum cut	Complete heart block, then re-establishment of sinus rhythm							
	80	0.24	0.11		0.040		0.000	
	80	0.24	0.11			0.055		0.040*

* At this time excitation of the remaining anterior epicardium in its midportion was 0.055 second after the onset of the reference QRS (see fig. 11).

values reported by these authors are smaller than those obtained in our study, the difference might be attributed to the different reference electrocardiograms and technic in mensuration. They had a few measurements from the left side of the septum immediately below the aortic valve where the excitation occurred the earliest, the deflection occurring as much as 0.0168 second before the onset of the R wave in lead II. Since the time of Lewis and Rothschild's important contributions, the concept

surface of the right ventricle was primarily dependent for its activation upon the left bundle, or that this area "belonged to the left ventricle." Contrariwise, in one animal they found a point on the left ventricular septal surface where the activation depended upon the right branch. Their conclusions as to whether these areas of the septal surfaces belonged to the right or left ventricle were based upon whether section of one or the other bundle branch was effective or ineffective in

TABLE 4.—*Both Free Walls Removed. Time, in Seconds, of Deflection Recorded From Proximity (Contiguous) Electrodes from Onset of QRS in Reference Tracing**

Rate	P-R	QRS	Right side of septum		Left side of septum	
			High	Low	High	Low
68	0.12	0.04	0.020		0.000	
68	0.12	0.04		0.000		0.002
68	0.12	0.04			0.000	0.000
Left side of septum cut						
68	0.14	0.06			0.040†	
68	0.14	0.06				0.030‡
68	0.14	0.06	0.015			
68	0.14	0.06		0.000		
Right side of septum cut—complete heart block, QRS 0.06 second						

* The horizontal lines indicate the sequence of measurements, those in the same line representing simultaneous recordings. The preparation from which these measurements were made is shown in figure 10.

† Above cut.

‡ Below cut.

delaying the excitation in that area. They reported findings consistent with ours concerning the delays in excitation in the basal areas of the septal surface following the production of bundle-branch block, and, though not specifically stated, it would seem that their upper place of exploration (point 3) was above the lesion made to produce the block. Their general conclusion that "the right side impulse arrives at the basal regions about 0.025 to 0.03 second after activation of the base of the anterior papillary muscle" is in accord with our studies.

The mechanism of the apparent apex-to-base direction has not been elucidated. A possible explanation would be a rapid conduction of the excitatory process through specialized tissue within the septum followed by a myocardial excitation in an apical-basal direction. The variations in the arrival of the excitatory process over different areas of the septal surface from animal to animal would be consistent with the presence of specialized tissue which did not have a stereotyped anatomic pattern from animal to animal. The present discussions must be limited to the dog, on which the present investigations were performed. The theory that direction of excitatory pathways is determined by the predominant direction of muscle fibers is not inconsistent with the present findings. We have carried out gross dissections of dog hearts and have noted that there are large muscle bundles streaming down the left side of the

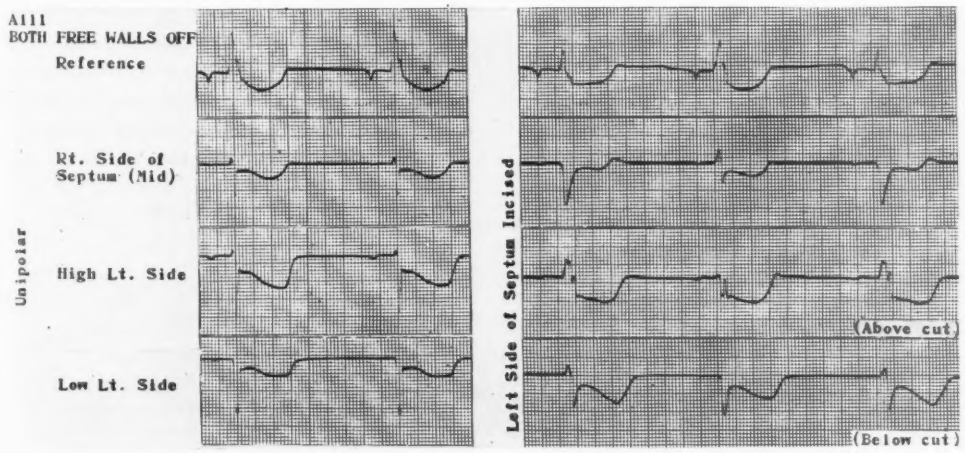

FIG. 9. Tracings obtained from a septum preparation as described, before and after an incision of the left septal surface. Evidence of later activation of the left side of the septum both above and below the cut is to be noted. One "escape" or nonblocked beat, however, occurred and was chosen for portrayal also; this beat is the central of the three beats.

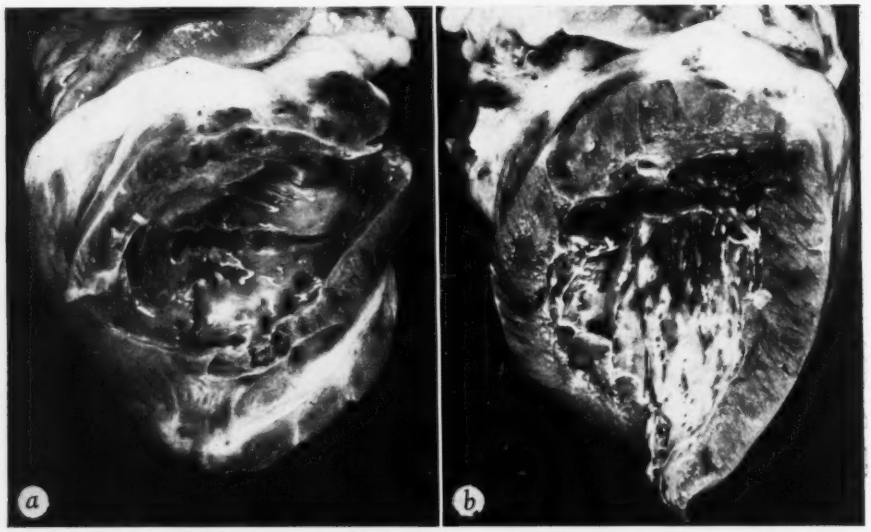

FIG. 10*a* and *b*. Right and left sides, respectively, of the standard preparation used, illustrating the extent to which the right and left ventricles have been removed. While much "purer" preparations of the wedge-shaped septum are possible, the success rate in regard to the maintenance of a sinus mechanism becomes small when the interventricular epicardial areas carrying the anterior descending and posterior descending coronary arteries are removed. The incisions in the ventricular septum shown are representative of those carried out in these investigations.

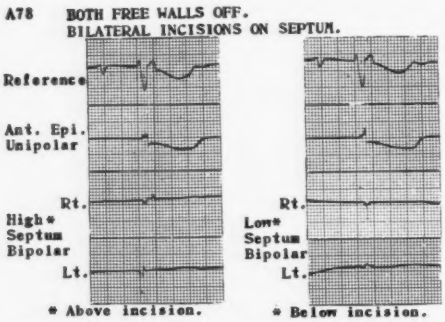

FIG. 11. Simultaneous records obtained from either side of the septum after bilateral incisions into the septum. The standard reference tracing indicates that the mean excitatory pathway is from base to apex, the reverse of that obtained without such injuries. The anterior epicardium is excited late, as are the other parts of the septal surface with the exception of the upper left surface. The double deflections obtained on the right upper surface were occasionally obtained with the proximity type of electrodes on the septum and exact interpretation is not possible; they suggest, however, that two areas relatively close to the electrodes were being excited at different time intervals.

septum which curl deeply and upward to approach the mid and upper surface on the right side. This would explain early excitation of the lower right surface of the septum after incision on the right side of the septum. Investigations carried out in the chicken embryo by Hoff and co-workers[7] have shown that the pattern of atrioventricular conduction is present very early in the development of the heart and if this were true for the mammalian heart then it is established before the ventricular septum is formed. It would be reasonable to suppose that the developing ventricular septum would be activated from its points of growth or from below, and this pattern might be maintained.

It is difficult to understand the results of Segers' report[8] wherein the whole ventricular septum of the isolated perfused rabbit's heart was removed without disturbance in intraventricular (or atrioventricular) conduction. It is believed that such results would never be obtained on the dog's heart.

An explanation must be sought for the initial potentials recorded from the intact heart, which are oriented so that the apical area is positive to the base, as illustrated by the large Q wave in our standard bipolar

reference electrocardiogram and the downward oriented loop in the vectorcardiogram. A possible explanation would be that these represented endocardial-to-epicardial spread in the apical area where the excitatory process has been demonstrated to be early, or tangential spread in other portions of the free walls adjacent to the septum. One of the uniform results of removal of large portions of the ventricular walls is that such early potentials, oriented so that apical environment is positive to the basal environment, disappear.

The increase in P-R interval (tables 2 to 4) following incision on the left side of the septum might be related to the transseptal delay consequent to the loss of normal excitatory pathway from left to right. In table 2 it is to be noted that the excitation of the right side of the septum, excluding the conus area, relative to the reference QRS has become earlier by the same amount as the P-R has been lengthened. Similar lengthening of the P-R interval in the left bundle-branch block has been noted by Sodi-Pallares and co-workers. The high incidence of prolongation of the P-R interval in left bundle-branch block as compared with right bundle-branch block has been re-emphasized by these authors. It may be noted that in a study by one of us (Burchell)[9] on interference dissociation with either right or left bundle block, it was in the latter that the P-R interval was regularly lengthened as compared with the instances when right bundle block was present. Delay in transseptal spread when the left side was blocked might be a better explanation than delay in a left bundle system in this case.

The marked suspectibility of the preparation to complete heart block when minor injuries are made on one side of the septum after the opposite side has been severely injured is further support of localized and specialized conduction tissue in those areas where the right and left bundles are said to exist. The exact disposition of such tissue needs further elucidation, however.

Conclusions

It has been possible to perfuse the isolated heart by the Langendorff technic and to remove large portions of the free walls of ventricles, allowing direct exploration of the surfaces of the ventricular septum in regard to its electrical activity. The excitatory process in the dog's ventricle is a very complicated process and does not follow the stereotyped and conventional bundle-branch and Purkinje system, with simple bilateral perpendicular excitation of the septum.

Evidence is presented to indicate unequivocally that the mean pathway of excitatory process is from apex to base.

Considerable variability in the time of excitation of the various areas of the right side of the ventricular septum was observed from preparation to preparation. The mid and lower surfaces of the right side of the septum closely followed the left side in the excitatory sequence.

Incisions into either side of the septum usually produced on the homolateral side delays in excitation of the septal surface above the injury as well as below it. The incision on the left side of the septum usually resulted in an increased duration of the P-R interval.

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Effects of Cardiac Glycosides upon the Electrical Activity of Single Ventricular Fibers of the Frog Heart, and Their Relation to the Digitalis Effect of the Electrocardiogram

By LOWELL A. WOODBURY, PH.D., AND HANS H. HECHT, M.D.

Using microelectrodes having an external diameter of less than 1 μ, potential variations of single cardiac fibers were obtained from frog ventricular muscle in situ. The normal membrane potential consists of a rapid depolarization and slow recovery, the latter occurring in three distinct phases. Digitalis glycosides alter profoundly the slopes of these various phases and drastically shorten the entire period of recovery. The characteristic cardiac action potential is thus converted into a spike which resembles the electrical events recorded for skeletal muscle or nerve. These changes occur independently of mechanical systole which remains essentially unaltered. The deformation of the action potential occurs uniformly throughout the ventricular muscle. They are related to the RS-T segment depression of the surface electrocardiogram which in this instance cannot be explained as being caused by a failure of the diastolic repolarization of the endocardial surface but must be an expression of uniform shortening of the entire process of recovery.

THE DEVELOPMENT by Gerard and his students[1–3] of a capillary ultramicroelectrode with an external diameter of less than 1 μ has led to a revival in interest in the electrical characteristics of single cells of various types of tissues.

The method has been employed to study the membrane resting and action potentials of single fibers of frog striated muscle,[1–8] frog sciatic nerve,[9] and isolated canine[10–12] and goat[12] Purkinje fibers. By means of appropriate modifications we have at this laboratory successfully applied the ultramicroelectrode technic to the intact beating heart. We have obtained records and described the electrical characteristics of single cardiac fibers in situ from frog ventricles[13–15] and embryonic chick hearts.[16, 17] This report presents the results of a study of the effects of digitoxin and other cardiac glycosides upon the membrane resting and action potentials of single ventricular fibers of the frog heart.

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Certain inferences may be drawn from these experimental findings concerning the effect of digitalis on the ventricular complex of the surface electrocardiogram, which consists of a depression of the RS-T segment and a shortening of the Q-T interval. The significance of these changes has remained obscure, and the superficial resemblance to the electrocardiogram in myocardial disease has led to the statement that the effect of digitalis on the heart muscle is essentially a harmful one.[18, 19] Macleod[20] has measured the duration of the excitatory state of the frog heart during administration of digitalis glycosides and has demonstrated a shortening of the electrical systole together with a decrease in the length of the refractory period similar in many respects to that obtained by the administration of acetylcholine. When a monophasic record was produced by injuring the surface of the ventricular musculature, again a striking decrease in the duration of the electrical systole occurred, giving the monophasic record a spike-like appearance. A similar loss of plateau of the monophasic record of injury with shortening of Q-T was also noted by Schellong and Stetzer using Schütz's technic for inducing monophasic action currents.[21] There exists a

relationship between records obtained from freshly injured regions yielding a monophasic response and those obtained by ultramicroelectrodes from the cell interior. Therefore, these observations are of interest and offer information on the basic significance of the digitalis effect of the electrocardiogram not generally yielded by a discussion of the superficial resemblances of electrocardiographic surface patterns.

Methods

The technic and the experimental methods used have been described previously[15] and reference should be made to that paper for details. Summer stage leopard frogs were used as experimental animals. The frogs were pithed, the chest opened and the animals placed in a plastic chamber through which Howell's frog heart Ringer's solution was circulating. A nearly constant temperature for any particular experiment was maintained but various experiments were run at different temperatures.

A series of normal control records was obtained from each preparation. Digitoxin or one of the other cardiac glycosides was then administered and tracings were recorded thereafter every few minutes up to five hours.

The various compounds were usually injected into the aorta or directly into the lumen of the ventricle. Since the digitoxin had been dissolved in 40 per cent alcohol it was diluted 10 times with frog Ringer's immediately before injection. Control injections of 4 per cent and 10 per cent alcohol up to a dose of 0.5 ml. failed to cause any observable changes. The dose of the glycosides varied. The maximum amount administered did not exceed 3.0 mg. per kilogram of the active substance. The maximum volume injected was about 0.5 ml., although the usual volume generally approximated 0.3 ml.

It seemed desirable to correlate the mechanical and the electrical events of the cardiac cycle, but since the usual methods of recording mechanical events of the heart do not work well with the intact heart connected to the circulation it was necessary to devise another method. The system finally used employed a special electromechanical transducer tube (RCA 5734) which has the property of converting extremely small mechanical movements into voltage changes. The tube has a movable anode connected to an external lever. A change in anode-cathode spacing results in a change in plate current and therefore in output voltage. A small plastic L-shaped foot with a small (0.4 mm.) hole in the center of the foot was fastened to a stiff piece of spring brass. The anode lever on the transducer tube was coupled to the stiff spring by a piece of weak spring. The tube is so sensitive that a reduction in amplitude was necessary. The plastic foot was lowered over the frog heart so that a light but firm contact was made. The contractions of the heart raised and lowered the foot slightly so that a movement was transmitted to the anode lever of the transducer tube which produced an output voltage proportional to the amplitude of movement of the frog heart. The microelectrode was inserted through the hole in the foot. In this way simultaneous records could be made of the electrical activity of a single fiber and of the movement of the heart.

The experiments were carried out with five different glycosides known to have digitalis-like actions. Digitoxin* was used most frequently with varying doses and under various conditions. The results obtained with digitoxin constitute the main body of this report. A limited number of observations were carried out with ouabain, scillaren B., lanatoside C, and K-strophanthoside.

Results

When a microelectrode, connected to a suitable recording system, is inserted into a single muscle fiber of a beating frog ventricle, a regular sequence of events is obtained.[15] With the microelectrode on the outside of the fiber an isoelectric base line is traced on the recording. When the needle penetrates the cell membrane during diastole a sudden voltage, negative with respect to the outside of the fiber, appears. This is the *membrane resting potential* (MRP). When electrical systole occurs this membrane potential rapidly falls to zero, and then reverses itself as the inside of the cell becomes positive with respect to the outside (overshoot). The sequence of disappearance and then reversal of the membrane voltage constitutes *depolarization* and corresponds to excitation of the cell. Following depolarization a slow period of *repolarization* or recovery ensues which returns the membrane voltage to its resting state. The sequence of depolarization and repolarization is known as the *membrane action potential* (MAP) to distinguish it from action potentials taken from the outside of the cell. When the microelectrode is withdrawn from the cell, whatever voltage is present disappears and an isoelectric base line is again recorded.

The period of excitation or depolarization is quite rapid and is an inverse function of the

* Digitoxin-Lilly.

temperature; the higher the temperature, the shorter the time required for depolarization.

We have pointed out previously that the period of repolarization or recovery of the heart fiber is composed of at least three separate phases differing from each other in rate, duration and response to changes in environmental temperature.[14, 15] The three phases of recovery and the other components of the membrane action potential are illustrated in figure 1.

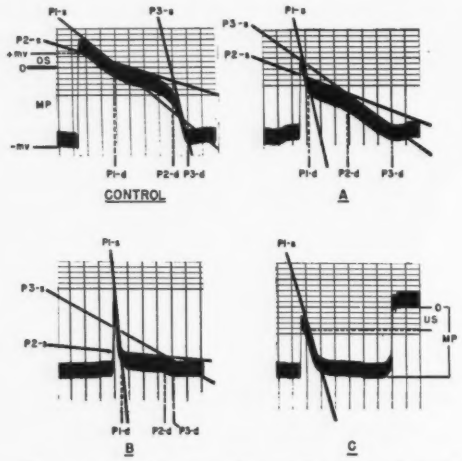

FIG. 1. Membrane action potentials of single ventricular fibers of the frog heart at different stages of digitoxin intoxication. Control: no digitoxin administered. *A:* early digitoxin effect. *B:* strong digitoxin effect. *C:* very strong effect, just before complete asystole.

P1-S, P2-S, P3-S, slope or rate of recovery of phase one, two and three respectively; P1-d, P2-d, P3-d, duration of phase 1, 2 and 3 respectively. OS: overshoot; US: undershoot or failure of complete repolarization. MP: membrane potential.

The duration of the normal action potential is an inverse function of the temperature, increasing in length as the temperature decreases. However, for any given temperature the action potential durations are quite constant. The rate of the heart beat increases with temperature, and in pithed frogs (vagosympathetic control removed) the logarithm of the rate is directly proportional to the logarithm of the reciprocal of the duration. This relationship affords a means of evaluating changes in duration of the action potential when the heart rate changes.[15]

Effects of Digitoxin

Duration of the Membrane Action Potential and its Components. When digitoxin is administered to the frog, the action potential duration as a whole may at first lengthen and then shorten or may shorten directly. In figure 2 are shown the changes of the total action potential duration with time in three experiments, exhibiting a mild, moderate and severe effect of digitoxin. In figure 2*A* transient lengthening followed by shortening is shown, in figure 2*B* there is a gradual but severe shortening, while in figure 2*C* a rapid extreme shortening ends in asystole. The net

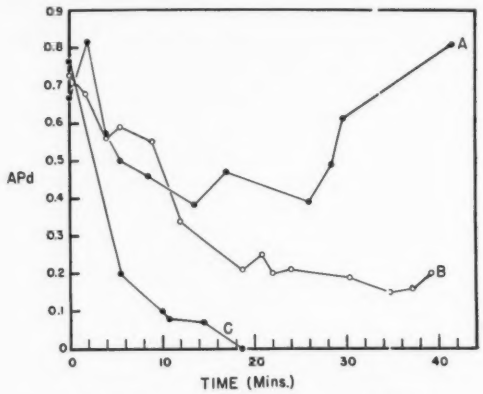

FIG. 2. Action potential duration (APd) as a function of time after administration of digitoxin. *A:* mild effect with recovery; *B:* marked effect, but no asystole; *C:* strong effect with rapid asystole. APd in seconds.

result of the digitoxin is to decrease the duration of the action potential.

The membrane action potential (MAP) consists of four components, the period of depolarization and the three phases of repolarization or recovery. The effect of digitoxin was studied upon the duration of these four components with the following results:

1. Depolarization: The period of depolarization is short compared with the period of repolarization. It ranges from about 29 milliseconds at 10 C. to about 14 milliseconds at 20 C. Since the deflection time of the string galvanometer used was about 5 milliseconds, measurements made at 20 C. or higher are in error. Preliminary studies indicated that there

were no effects of digitoxin upon the duration of depolarization that could be detected with the equipment used.

2. Repolarization: The primary effect of digitoxin is upon the duration of the repolarization process. Since repolarization is composed of three separate phases[14, 15] it was necessary to establish the normal pattern before a detailed analysis could be made.

At all temperatures, phase 2 (the "plateau" of the monophasic curve) had the longest duration, phase 1 the next longest and phase 3 the shortest. At any given temperature the relation between the durations of the three phases in a normal heart is quite constant. Digitoxin modifies this relation profoundly. With large doses phases 2 and 3 apparently disappear completely; with moderate doses the relations among duration of the phases change. If the relations among the various phases remained constant during digitoxin the correlations between the phases would be positive and of moderately high value. A low correlation or a high negative correlation would indicate a change in the relation of the various phases to each other. Table 1 shows the correlations obtained among the various phases during the time course of a small dose of digitoxin. As may be seen from the correlations there was a dissociation between phase 1 and 2 and between phase 2 and phase 3. The high negative correlation between phase 1 and phase 3 indicates that under the influence of digitoxin the duration of these two phases changes in opposite directions.

TABLE 1.—*The Influence of Cardiac Glycosides upon the Three Phases of Recovery of the Action Potentials of Single Cardiac Fibers. Correlation among the Duration of these Phases under the Influence of Digitoxin.*

Correlation between duration of	r	p	Significance
Phase 1 and Phase 2.....	+0.25	0.1	none
Phase 2 and Phase 3.....	−0.16	0.1	none
Phase 1 and Phase 3.....	−0.75	0.001	high
Phase 1 and Phase 3, Phase 2 eliminated.....	−0.74	0.01	high

Figure 3 illustrates the changes in the duration of the action potential and the various phases following a small dose of digitoxin. As may be readily seen the changes in phase duration do not parallel each other. The parallelism of phase 2 and the total action potential durations is explained on the basis that phase 2 constitutes a large portion of the total.

In summary it may be noted that under the influence of moderate doses of digitoxin the action potential shortens markedly. The major part of the shortening takes place in phase 2. Phase 3, however, lengthens and phase 1 shortens. With recovery these processes reverse.

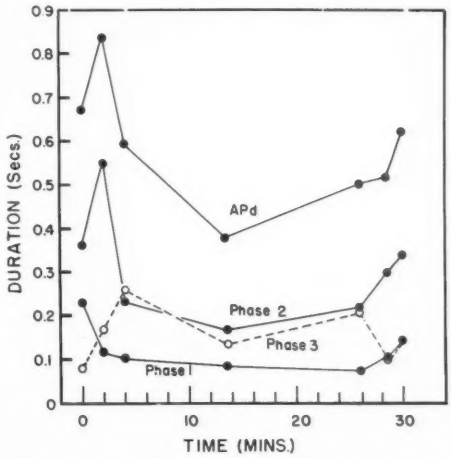

FIG. 3. Duration of the action potential (APd) and the various phases of recovery as a function of time after the administration of digitoxin.

Changes in Rate of Recovery (Slope) of the Three Phases. Under ordinary conditions the three phases of recovery have different slopes. Under the influence of digitoxin the rate of recovery of the first phase becomes greater (the slope becomes steeper) while the rate of the third phase becomes slower (the slope becomes flatter) (fig. 1). The slope of phase 2 remains relatively unchanged.

With comparatively large single doses of digitoxin (1 to 2 mg. per kilogram) the effects are more striking. The slope of the first phase becomes steeper and those of the second and third phase become flatter. Eventually the second and third phase disappear and re-

covery is apparently taken over by the first phase. Figure 1 illustrates these gradual changes from a normal action potential to the stage at which apparently only the first phase remains.

Under the influence of digitoxin there is a strong negative correlation ($r = -0.818$, $p < 0.001$) between the duration of the action potential and the rate of recovery of the first phase, that is, as the action potential duration shortens the slope of the first phase steepens. Whether either of these is a function

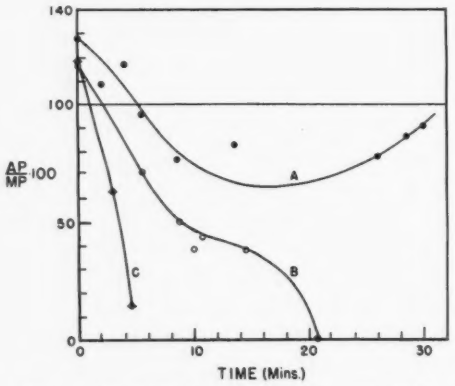

FIG. 4. Changes in the relative amplitude of membrane resting (MP) and membrane action potentials (AP) under the influence of digitoxin. The relative amplitude is expressed in terms of the action potential as a percentage of the membrane resting potential. When the ratio is greater than 100, overshoot is present. When less than 100, undershoot or failure of complete depolarization is present.

A: Mild effect of digitoxin with partial recovery. *B:* Marked effect with eventual failure of depolarization and asystole. *C:* Strong effect with rapid decrease in amplitude of action potential.

of the other or whether both are dependent upon some other factor could not be determined.

Changes in Membrane Voltage. The amplitude of the membrane resting and the membrane action potentials of single fibers of the frog heart vary from fiber to fiber and from frog to frog. Within the limits of detectability there is no significant change with temperature or time under normal conditions. Moderate and large doses of digitoxin, however, produce alterations in the amplitude of the membrane *action* potential while leaving the membrane *resting* potential comparatively unaffected. The changes in *amplitude* of the membrane action potential appear somewhat later and recover earlier than the changes in *duration*. The general pattern of change in voltage due to digitoxin is shown in figure 4. The action potential is plotted as a percentage of the amplitude of the membrane potential against time after a dose of digitoxin. Three curves are shown, illustrating mild, moderate and severe effects of digitoxin. As can be seen from the curves the general pattern consists in a disappearance of the overshoot followed by *undershoot* or failure of the cell to depolarize completely. With mild doses recovery ensues. With large doses the effect continues until the action potential disappears; the cell is then in asystole but the membrane potential is still present.

Treating the difference between the membrane action potential and the membrane resting potential as overshoot and assigning an appropriate sign to it (positive or negative), we calculated correlations among the overshoot (as a percentage of the membrane potential), action potential duration, and the rate of recovery of phase 1. There was a moderate correlation (0.568; $p < 0.02$) between the per cent overshoot and the duration of the action potential. There was a high negative correlation (-0.818, $p = 0.02$) between the action potential duration and the rate of recovery (slope) of phase 1 and a nonsignificant correlation (-0.321, $p > 0.1$) between per cent overshoot and the rate of recovery of phase 1. Partial correlations by eliminating each of the variables in turn did not change the direct correlations significantly.

The correlation between per cent overshoot and action potential duration under the influence of digitoxin is noteworthy. For another group of experiments the correlations between action potential duration and per cent overshoot are illustrated in table 2. There is a progressive increase in magnitude of the correlation between these two variables as the digitoxin effect becomes greater. The correlation probably indicates that both changes are consequent upon some hitherto undisclosed mechanism.

Relation of Mechanical and Electrical Events. By use of the apparatus described above, the mechanical movement of the heart was recorded simultaneously with the membrane action potential of single fibers from the middle area of the ventricle. A record showing simultaneous recordings of the action potential and the mechanical events of the heart is shown in figure 5. The ordinate of the mechanical event sequence is essentially the change in diameter of the ventricle caused by contraction. The first peak is the change in ventricular diameter caused by the inflow from the auricle and is called the auricular peak. The second peak is that caused by the contraction of the ventricle. Occasionally a third peak caused by contraction of the conus is seen.

TABLE 2.—*Correlations between Per Cent Overshoot and Action Potential Duration for Various Effects of Digitoxin.*

Item	r	p	Significance
Control experiments	−0.078	0.1	no
Mild effect	0.312	0.1	no
Severe effect	0.617	0.001	yes

Figure 5 shows that the ventricular contraction commences shortly after the depolarization of the fiber. The peak of ventricular contraction is reached at a time depending on the temperature. It averages 0.11 second at 26 C. Following the peak of contraction the muscle relaxes and returns to its resting stage. Relaxation is completed just after the end of the action potential. Duration of the ventricular contraction is defined here as the time from the onset of depolarization of the fiber to the end of the relaxation of the muscle. This definition was adopted because the actual time at which the ventricle starts to contract is obscured by the inflow of blood from the auricles. When it was possible to determine with some certainty the onset of ventricular contraction it was found that this followed the depolarization by about 10 to 20 milliseconds, a time lag which is negligible compared to the normal duration of contraction which varies from 500 to 2500 milliseconds, depending on temperature.

Records of ventricular contraction were made simultaneously with single fiber recordings at temperatures ranging from 12 to 26 C. When the ventricular contraction duration (VCd) was plotted against the action potential duration (APd), for normal control records a straight line was obtained as shown in figure 6. The equation was (VCd) = 1.195 (APd) −0.054. The intercept of −0.054 is significantly different from zero and the slope of 1.195 is significantly different from 1.

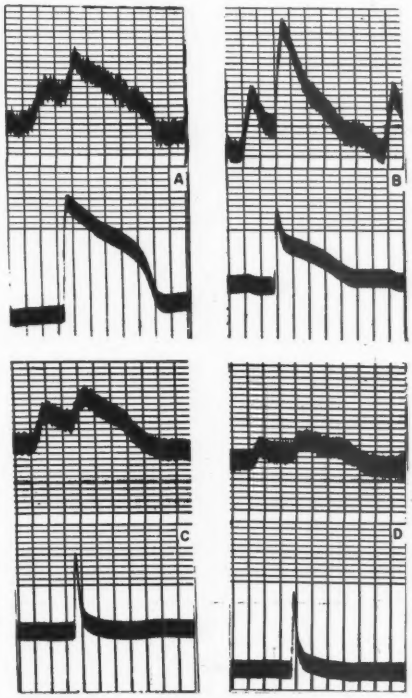

FIG. 5. Mechanical events of the whole heart and electrical events of single ventricular fibers. Upper line mechanical record, lower line electrical record. In the mechanical record, the large peak is the result of ventricular contraction. The preceding elevation represents the change in ventricular diameter caused by inflow from the auricle.

A: Control record, no digitoxin. *B, C, D:* progressive changes following administration of 1.2 mg. per kilogram of digitoxin. Note that the duration of the action potential shortens markedly with little change in the duration of the mechanical events.

When effective doses of digitoxin are given there is a shortening of action potential duration (APd) but only a small, if any, change in ventricular contraction duration (VCd). The

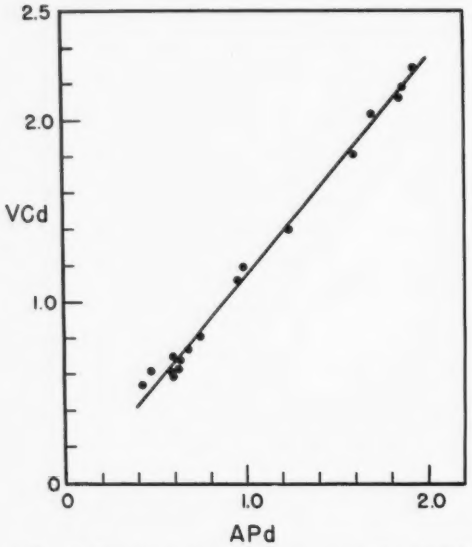

FIG. 6. Duration of ventricular contraction (VCd) in seconds versus action potential duration (APd) in seconds in normal control records. Line fitted by method of least squares.

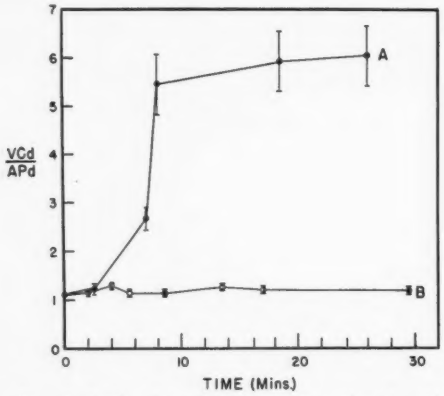

FIG. 7. Ratio of ventricular contraction duration (VCd) to action potential duration (APd) as a function of time after digitoxin for two dose levels. *A*. 2.0 mg. per kilogram; *B*. 1.2 mg. per kilogram.

net result is that the ratio between these two events (VCd/APd) increases. In figure 7 the change of this ratio as a function of time after digitoxin is shown for two dose levels. At the 1.2 mg. per kilogram dose level (*B*) only minor fluctuations of the ratio occurred. At the 2 mg. per kilogram level (*A*) there was a sudden change in the ratio indicating an extreme decrease in the duration of the action potential compared to the ventricular contraction duration. Figure 5 shows typical records of the 2.0 mg. per kilogram dose experiment. As may be seen, the effective duration of the action potential shortens markedly, but the ventricular contraction remains about the same in duration. The changes in the amplitude of the

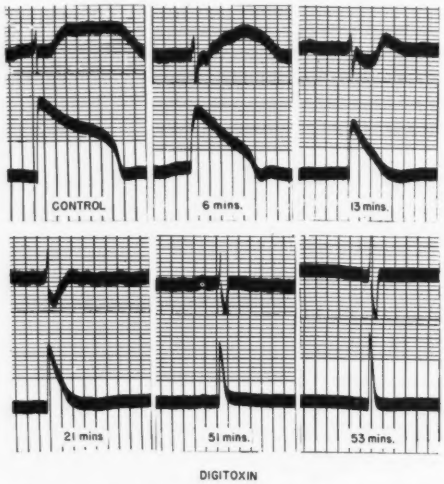

FIG. 8. Simultaneous records of surface electrocardiogram and single fiber membrane action potentials. Times following injection of single dose of digitoxin. Note progressive RS-T segment depression in surface record simultaneous with increase in rate of recovery process. See text.

ventricular contraction shown in figure 5 are real but are not necessarily proportional to the force of the contraction.

Under the influence of digitoxin, the ends of the mechanical and electrical events become dissociated. The ventricular contraction stays about the same in duration but the action potential shortens markedly. The action potential serves to initiate the contraction but does not, apparently, play an absolutely necessary part in the rest of the contractile process. In figure 5*C* the action potential has recovered to the extent of 80 to 90 per cent by the time the contraction has reached its peak, so that it

is clear that the action potential need not be integrally concerned in the heart's contractile process other than to initiate it.

Surface Electrocardiogram. Figure 8 shows simultaneous recordings of membrane action potentials from a single fiber and surface electrocardiograms taken within a millimeter or less of the single fiber. The figure shows the parallel change caused by digitoxin in the membrane action potential and in the surface electrocardiogram. The auricular and the conus components of the whole heart electrocardiogram are not visibly present because of the small size of the electrode and its closeness to the ventricular surface.

The QRS complex corresponds to the depolarization of the fiber and the remainder of the electrocardiogram to the recovery part of the action potential of the fiber. Since the monophasic record is that of a single fiber and the surface electrocardiogram that of many fibers, a close time correspondence is not to be expected.

Measurements of the rate of recovery, after digitoxin took effect, and the magnitude of the RS-T depression were correlated. The correlation was 0.91 ($p < 0.001$) and was highly significant.

Effects of Other Cardiac Glycosides

The other cardiac glycosides tested were ouabain, scillaren B, lanatoside C and K-strophanthoside. Four experiments were performed using ouabain, two using lanatoside C,* one using scillaren B, and one using K-strophanthoside. The results may be summarized by saying that, within the limits of variation of the data, their effects were indistinguishable from those of digitoxin. Small quantitative differences may exist but were not found in these experiments.

Discussion

The impalement of a single fiber by an ultramicroelectrode permits the recording of the electrical events of a single fiber. We have demonstrated by this technic a peculiar but perhaps not entirely specific action of digitalis compounds on the rate of recovery from excitation which is drastically shortened, and on the various phases of repolarization, which are changed in a predictable fashion (figs. 1, 5, 8).

A fundamental difference between skeletal muscle and cardiac muscle is the long duration of the recovery process of the cardiac muscle. In skeletal muscle the action potential lasts only a few milliseconds; in cardiac muscle it may last for 0.4 to 6.0 seconds depending on the temperature. In skeletal muscle the action potential serves only to initiate contraction. In cardiac muscle the action potential not only initiates contraction but endures for almost the whole period of contraction.

One effect of digitoxin in the normal frog heart in situ is to shorten profoundly the duration of the action potential without greatly affecting the duration of the contractile process. This results in a dissociation of the terminal electrical and mechanical events. With toxic doses of digitoxin the action duration may become merely a spike and, except for the time scale, the picture of the action potential and the muscular contraction resembles those of striated muscle.

The long duration of the action potential is paralleled by a long refractory period. McLeod[20] has shown that for the frog heart the refractory period is just slightly shorter than the action potential and that as the action potential duration shortens under the influence of cymarin (a cardiac glycoside) the refractory period shortens in a parallel fashion ($r = 0.983$, $p < 0.001$). The shortening of the action potential and the concomitant decrease in the refractory period would suggest that the heart could be thrown into tetanus at this stage.

It is interesting that digitoxin had a different effect upon each of the three phases of recovery. The rate of repolarization (slope) of phase 1 was increased, that of phase 3 was decreased and that of phase 2 was comparatively unaffected. With increasing doses of digitoxin, however, the slopes of phase 2 and 3 become zero and phase 1 takes over all of the recovery process. The reason for these various changes is obscure. We have suggested[14, 15] that the three phases of recovery

* Cedilanid (Sandoz).

depend upon different metabolic processes, and it may be that digitoxin interferes with each of these processes in a different manner.

The gradual disappearance of the action potential, with loss of overshoot and later failure of the fiber to depolarize, but with the membrane potential comparatively unaffected, are reminiscent of other substances than digitoxin. Toman, Woodbury and Woodbury[22] have shown that both di-isopropyl fluorophosphate (DFP) and eserine caused the surface action potential of a frog sciatic nerve to decrease and eventually to disappear while the demarcation potential remained relatively unchanged. The same effect has been shown for procaine on frog nerve by Bennet and Chimberg.[23]

Potassium chloride, on the other hand, will abolish the action potential and the overshoot, but at the same time cause a decrease in the membrane potential, both in frog sciatic nerve[22] and in single fibers of the frog heart (personal observation).

Daly and Clark[24] pointed to a remarkable similarity of the effect of strophanthin on the intact heart to that of lack of sodium. On isolated frog sartorius muscle, on a single nerve preparation and on isolated Purkinje tissue,[12] a decrease in concentration of sodium resulted in loss of overshoot roughly proportional to the logarithm of the extracellular sodium concentration. In the latter preparation, a shortening of the duration of the action potential was likewise present. No consistent changes in resting membrane potentials were noted in any of these experiments.

Surface electrocardiograms taken from the ventricular surface showed changes that could be correlated with simultaneously recorded ventricular single fiber records. As the duration of the action potential decreased the Q-T interval decreased. As the slope of the first phase of recovery increased the RS-T segment became depressed. The correlation between the slope of the first phase and the magnitude of the RS-T depression was 0.91 ($p < 0.001$). In the advanced toxic stages of digitoxin action extreme shortening of Q-T results in RS-T changes of a peculiarly exaggerated kind.

The origin of the surface electrocardiogram is a complex subject involving, as it does, volume conduction effects, time and space summation of the activities of thousands of fibers and the derivatives of the membrane action potential. It is interesting to note that the correlation of the rate of recovery of phase 1 and the RS-T depression is extremely high. The implication is that the RS-T depression in digitoxin intoxication in the frog is merely a reflection of the increased rate of recovery of the heart.

For the mammalian heart, differences in the length of the excitatory state are known to be responsible for deviation of the R-T junction and for the shape of the T wave of the surface electrocardiogram. A delay of repolarization with localized lengthening of the excitatory state occasioned, for instance, by injury of subendocardial or of subepicardial regions of the heart is known to result in displacement of the RS-T segment and in T-wave changes.[25, 26] A similar explanation has been advanced for the digitalis effect of the human electrocardiogram.[27, 28] Our observations on the electrical events of single heart muscle fibers recorded simultaneously with surface electrocardiograms have, however, demonstrated that the RS-T segment changes of the electrocardiogram of the frog following digitalis medication are an expression of a uniform shortening of the excitatory process throughout cardiac musculature. It appears then that a more or less *uniform shortening* of repolarization following digitalis therapy results in RS-T segment depression in surface records which, except for the Q-T interval, resemble those apparently caused by *localized lengthening* of repolarization characteristic of myocardial disease.

Biphasic records of single fibers resembling the surface electrocardiogram may be obtained by plotting the rate of rise and fall of the monophasic action potential. The surface action current may be considered the first derivative of the membrane action potential. Generally speaking, the cell potential measured by the technic here used is defined as stored energy (charge). The current flowing over the cell (the surface action current) is a measure of the rate at which the charge is changing. Therefore, a change in the rate of recovery of the

action potential should be roughly proportional to the depth of the R-T junction depression. The peculiar superficial resemblance of the electrocardiogram of severe myocardial disease to that induced by digitalis therapy at a time when cardiac function is usually improved resolves itself nicely when it is considered that the surface electrocardiogram may be altered if (a) the length of the excitatory state is made to differ significantly in various parts of the heart, or if (b) the rate of the repolarization is uniformly shortened throughout the heart. Combined effects are likely to occur, but the over-all length of the excitatory state, the Q-T interval, long in (a), short in (b), may separate one from the other.

Summary

1. The changes in membrane resting and action potentials of single cardiac muscle fibers of the frog heart in situ were examined before and after the administration of digitoxin, ouabain, scillaren B, lanatoside C and K-strophanthoside. No obvious differences in response were noted for any of the compounds studied.

2. The major effects noted may be summarized as follows: The duration of depolarization is not affected but repolarization is profoundly altered so that the duration of the membrane action potential is markedly shortened. After toxic doses of digitoxin, the record assumes a spike like appearance.

3. The three separate phases of recovery, previously described by us, are altered and the rate of recovery of the three phases is changed in a characteristic manner: the slope of the first phase becomes steeper, that of the second and third flatter. Eventually, the second and third phases disappear and recovery is apparently accomplished by the first phase alone.

4. Recovery may commence before depolarization has been completed and the depolarization deflection appears prematurely arrested (undershoot).

5. These changes are independent of mechanical events. Mechanical movements simultaneously recorded with the membrane action potential remained relatively unchanged in the face of pronounced alterations of the membrane action potential.

6. The steepening of the first phase shows a high correlation ($r = 0.91$) with the magnitude of the RS-T depression in simultaneously recorded surface electrocardiograms. It is assumed that the uniform shortening of the repolarization process caused by cardiac glycosides results in RS-T segment depression which, except for the Q-T interval, resembles the changes apparently caused by localized lengthening of repolarization characteristic of myocardial disease.

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Studies of Electrocardiographic Changes during Exercise (Modified Double Two-Step Test)

By PAUL N. G. YU, M.D., AND ALFRED SOFFER, M.D.

A method of recording electrocardiograms *during* the performance of a double two-step exercise test is described. Data obtained from 32 normal subjects and 54 patients are analyzed, and changes in heart rate, S-T segment, T wave and Q-T interval and the occurrence of premature beats described. Criteria for an abnormal response indicating coronary insufficiency are defined. This method retains the merits of Master's original test and in addition has several distinct advantages.

STUDIES of the electrocardiogram during and after exercise (walking on a treadmill ergometer at standard speed and grade) in normal subjects have shown a definite pattern of change in the Q-T interval and no evidence of coronary insufficiency.[1, 2] On the other hand, a large percentage of patients with various cardiopulmonary diseases showed definite and striking abnormal changes.

Since Master's "two-step" test[3, 4] has been widely used in different clinics, similar studies of the electrocardiogram *during* exercise were undertaken with modification of the original method. It is the purpose of this report to describe the procedure and to present the results obtained in 32 normal subjects and 54 patients with various cardiovascular disease. These studies suggest that the modified method can be used wherever the exercise electrocardiogram is indicated and that it contributes significantly to its sensitivity and safety.

METHOD

An exploring precordial electrode connected with the chest wire was placed over the fifth intercostal space along the left midclavicular line or slightly to its left. An indifferent electrode connected with the left leg wire was placed just below the tip of the right scapula. A third electrode connected with the right leg wire, placed over the right precordium, served as the ground. The exploring and indifferent electrodes constitute the so-called "CB_4" lead which was first introduced by Wolferth and Wood[5] and later modified by Lieberson and Liberson.[6] All three electrodes were tightly applied to the chest wall by a rubber chest strap* so that during exercise there was no change in the position of the electrodes. The control knob was switched to CF to record lead CB_4 or CB_5.

A portable direct-writing electrocardiograph (Edin) was used throughout the study. Changes in the electrocardiogram during and after exercise could be observed minute by minute. Lead CB_4 was standardized so that 1 mv. caused a deflection of 10 mm. If the QRS complex was too high, it was standardized at a deflection of 5 mm. per millivolt.

A short strip of lead CB_4 was taken before the exercise was performed. If the R wave was low and S wave deep (rS), the precordial electrode was moved further to the left until an Rs, or qRs complex was obtained. (Depression of the S-T segment is usually more marked with a high R wave than with a deep S wave, because the presence of a high R wave indicates that the electrode is facing the left ventricular surface.) The subject was instructed to take several deep inspirations and expirations while a tracing was being recorded. Marked shifting of the baseline or muscular interference indicated the need for tightening of the rubber chest strap and reapplication of the electrode paste. During exercise the baseline often wandered slightly due to respiratory movement. In some women it was necessary to place the exploring electrode in the anterior axillary line (CB_5) in order to obtain full phase contact of the electrode.

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* Obtained from Sanborn Company, Cambridge, Mass.

The performance of the step test was the same as that described by Master and associates[3, 4] except for the following modifications: (a) The CB_1 or CB_5 lead was used throughout the test and no tracings from limb leads were made. (b) A double two-step test lasting three minutes was performed on every subject unless it was interrupted by the appearance of symptoms or marked electrocardiographic abnormalities. (c) The tracings were made at rest, at the end of each minute during exercise, 30 seconds, 90 seconds, and 150 seconds after termination of exercise and 8 minutes after exercise or later.

The test was arbitrarily divided into four periods: (1) Resting—before exercise, (2) Exercise—three minutes or less. (3) Early recovery—first three minutes of recovery. (4) Late recovery—eighth minute of recovery or later.

The heart rate was obtained by measuring the number of QRS complexes in a period of six seconds and multiplying by 10. Depression or elevation of the S-T segment was measured from the iso-electric level (P-R or P-Q level). It was essential to measure three or four beats on a horizontal level in order to avoid simulation of S-T depression or elevation by a wandering baseline. The amplitude of the T wave was measured from the baseline to the peak of the wave in each individual complex. If there was distinct variation of the amplitude of the T wave, the average of the amplitude of an equal number of high and low T waves was recorded. Usually three or more consecutive Q-T intervals and corresponding cycle length were measured to the nearest 0.05 second. Their average values were used to compute the Q-T/T-Q ratio and the corrected Q-T interval ($Q\text{-}T_c$). The T-Q interval is the difference between the cycle length and its Q-T interval. The corrected Q-T interval ($Q\text{-}T_c$) was calculated from the modified Bazett's formula,[7]

$$Q\text{-}T_c = \frac{\text{Q-T interval}}{\sqrt{\text{cycle length}}}$$

Results in Normal Subjects

Thirty-two normal individuals between ages 24 and 66 years served as controls. They were mainly physicians, medical students, nurses, and technicians. There were 26 males and 6 females. None had a history of cardiovascular disease. Each had a normal physical examination and resting electrocardiogram. A roentgenogram of the chest was obtained in most of the subjects and was normal in each instance.

Changes in the heart rate varied greatly in different individuals. The maximum heart rates during exercise and early recovery were, respectively, 158 and 125 per minute, and these were recorded in the same subject. The heart rate returned to within 10 points of the resting value during the second minute of recovery in 25 of the 32 normal subjects. In several subjects the heart rate was the slowest in the second minute of recovery.

The Q-T/T-Q ratio at rest was usually less than 1. It always increased during exercise and promptly returned to the resting value before the third minute of recovery. In none of the normal subjects did the Q-T/T-Q ratio exceed 2 during exercise. The increase in average exercise Q-T/T-Q ratio was usually less than 100 per cent of the average resting value.

The pattern of changes of the $Q\text{-}T_c$ interval was the same as that observed in treadmill walking, that is, prolongation during exercise, shortening during early recovery and return to the resting value during late recovery.[1] The $Q\text{-}T_c$ interval was usually highest in the first minute of exercise. In no case during exercise did the $Q\text{-}T_c$ interval decrease below the average resting value. Shortening of the $Q\text{-}T_c$ interval during early recovery was definite, especially during the second minute of recovery.

There was no significant change in the P wave during and after exercise. Some individuals showed slight decrease in the amplitude of the R wave and a concomitant deepening of the S wave during exercise. The T wave became lower or remained unchanged during exercise in all of the instances, while in some subjects it increased slightly during early recovery. High T waves during exercise or early recovery, with an increase in amplitude of more than 50 per cent of the resting value, were not observed. Slight S-T depression of less than 1 mm. during or immediately after exercise occurred in four subjects. In a great majority of normal subjects the S-T segment remained iso-electric throughout the test. In two normal subjects a slightly elevated S-T segment at rest became iso-electric during and after exercise. We agree with Master[4] that this change should be considered as normal, unless the depression is below the iso-electric level. No S-T elevation has ever been noted in normal controls. None of the normal

subjects showed ventricular premature beats, auriculoventricular or intraventricular block, or the appearance of a Q wave during or after exercise.

Typical tracings of control subjects with normal response to exercise are illustrated in figure 1. The composite data of the heart rate,

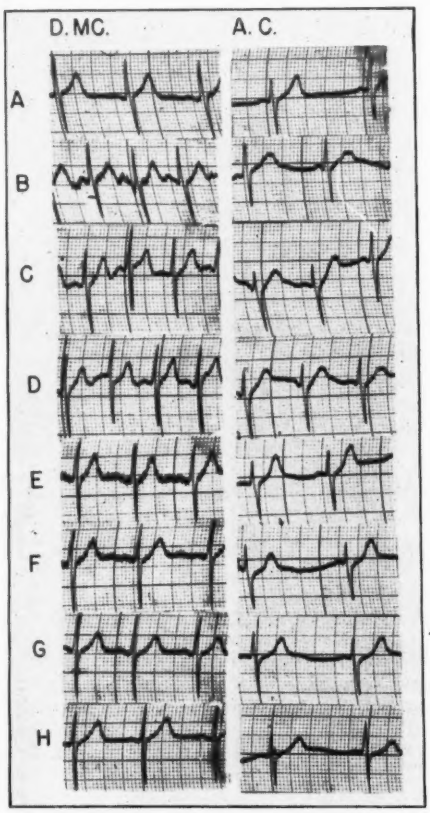

FIG. 1. Normal Subjects: D. Mc., male, age 46; A. C., male, age 30. *A*—Rest. *B, C, D*—Three minutes of exercise. *E, F, G*—First three minutes of recovery. *H*—Eighth minute of recovery.

Q-T/T-Q ratio and Q-T_c interval are presented in table 1.

On the basis of the electrocardiographic findings in normal subjects, abnormal responses in lead CB_4 or CB_5 were judged according to the following criteria: (1) Depression of S-T segment of more than 1 mm. below the isoelectric level. (2) (a) Partial or complete reversion of T wave (from upright to inverted or iso-electric, or from inverted to upright). (b) Increase in the amplitude of the T wave greater than 50 per cent of the resting value. (3) Q-T/T-Q ratio of more than 2.2 during exercise. (4) Shortening of the Q-T_c interval during exercise or prolongation of Q-T_c interval during early recovery. (5) The appearance of ventricular premature beats during exercise or early recovery.

We have not encountered intraventricular or auriculoventricular block.

TABLE 1.—*The Heart Rate, Q-T/T-Q Ratio, and Q-T_c in 32 Normal Subjects*

Period of Observation	Heart Rate Per Minute	Q-T/T-Q	Q-T_c
	Average and Range	Average and Range	Average and Range
Resting	78	0.90	.408
Exercise	57–98	.62–1.17	.358–.453
1st minute	114	1.58	.441
	79–140	.81–2.00	.367–.500
2nd minute	124	1.61	.430
	102–150	1.03–2.00	.384–.481
3rd minute	127	1.63	.430
	107–158	1.16–2.00	.372–.454
Early recovery			
1st minute	98	1.02	.393
	73–125	0.60–1.40	.342–.431
2nd minute	80	0.90	.400
	54–109	0.54–1.20	.369–.442
3rd minute	83	0.92	.405
	55–116	0.56–1.36	.367–.456
Late recovery			
8th minute	83	0.97	.415
	60–108	0.66–1.38	.360–.456
10th minute	82	0.95	.409
	66–113	0.64–1.36	.375–.448

RESULTS IN PATIENTS

Fifty-four patients ranging in age from 18 to 69 years were studied. There were 35 males and 19 females. They were classified into three main groups according to diagnosis. (a) Group I—21 patients with a typical history of angina pectoris. (b) Group II—21 patients with arteriosclerotic and hypertensive heart diseases (ASHD and HCVD) who had no history of angina. (c) Group III—12 patients with miscellaneous diseases including five with rheumatic heart disease, two with congenital heart disease, two with intermittent

claudication, two with atypical chest pain and two with abnormal ballistocardiogram.

The resting electrocardiogram was normal in each instance except for minimal T wave abnormalities in six patients and slight S-T depression in one patient. Eleven patients in group I and four patients in group II did not complete the double two-step test because of precordial pain, severe dyspnea, or marked electrocardiographic changes. At least one exercise electrocardiogram was recorded for each patient. Two or more exercise tests were performed at regular intervals on nine patients.

TABLE 2.—*The Heart Rate, Q-T/T-Q Ratio, and Q-T_c in 54 patients*

Period of Observation	Heart Rate Per Minute	Q-T/T-Q	Q-T_c
	Average and Range	Average and Range	Average and Range
Resting	82	0.96	.417
	52–100	.61–1.56	.348–.486
Exercise			
1st minute	123	1.91	.447
	78–166	1.00–4.42	.385–.545
2nd minute	134	2.16	.447
	90–172	1.13–5.00	.399–.534
3rd minute	142	2.16	.438
	91–182	1.07–4.00	.375–.490
Early Recovery			
1st minute	112	1.50	.425
	69–166	.62–4.00	.364–.505
2nd minute	99	1.22	.426
	67–133	.67–2.60	.342–.495
3rd minute	91	1.17	.430
	59–124	.62–.2.26	.370–.510
Late Recovery			
8th minute	90	1.11	.430
	65–118	.63–1.70	.375–.490
10th minute	88	1.19	.437
	64–122	.74–1.78	.394–.490

Pulse and Q-T Changes

The average value and range of the heart rate, Q-T/T-Q ratio, and Q-T_c interval during rest, exercise and recovery are presented in table 2. The over-all heart rate in the corresponding minutes was higher in the patients than in the normal subjects. During exercise the heart rate of 15 patients exceeded 158 per minute which is the maximum rate obtained in the normal subjects. The heart rate failed to return to within 10 points of the resting value during the second minute of recovery in more than 75 per cent of the patients.

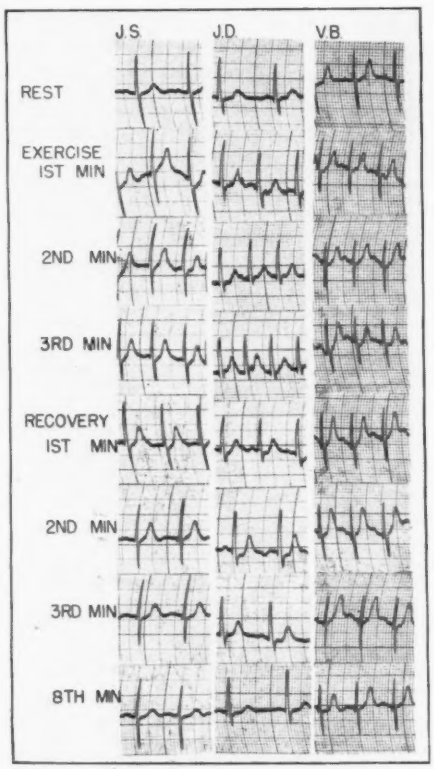

FIG. 2. *J. S.* A 58 year old woman with severe hypertension and history of angina pectoris. Note definite S-T depression during exercise which is less distinct during early recovery. There is also a significant increase in the amplitude of the T wave during both exercise and early recovery. *J. D.* A 44 year old man with typical history of angina pectoris. Note significant increase in the amplitude of the T wave during exercise and early recovery. The Q-T/T-Q ratio during exercise exceeds 4.0. Distinct S-T depression occurs during the first three minutes of recovery. *V. B.* A 54 year old woman with no evidence of cardiovascular disease. Although the increase in the heart rate during exercise (158 per minute) is comparable with that in case J. D., yet the Q-T/T-Q is less than 2.0. Furthermore, no significant changes in either the T wave or the S-T segment were observed.

The average Q-T/T-Q ratio in the corresponding minutes was higher in the patients than in the normal subjects. In 23 patients

the Q-T/T-Q ratio was more than 2.2 in one of the three minutes of exercise. In several patients who showed marked symptoms and distinct electrocardiographic changes, the exercise Q-T/T-Q ratio reached 4 or 5 (fig. 2, J. D.).

Although the averaged Q-T_c interval was prolonged during exercise, it did not shorten during early recovery. This abnormal response was observed in almost half of the patients.

three patients. In one patient multiple premature ventricular beats developed during the first minute of exercise and the patient did not complain of precordial pain until the end of the third minute (fig. 7).

Of the 21 patients in Group II, four showed distinct S-T depression during recovery and not during exercise, and eight exhibited similar changes both during exercise and recovery. Two patients had significantly high T waves

TABLE 3.—*Incidence of Abnormal Changes During Exercise and Recovery in 54 Patients*

	S-T Depression			Changes in T Wave*			Abnormal Q-T/T-Q Above 2.2	Abnormal Q-T_c	Ventricular Premature Beats
	During Exercise only	During Recovery only	During Exercise and Recovery	During Exercise only	During Recovery only	During Exercise and Recovery			
GROUP I Angina Pectoris (21 cases)	5	2	10	4 2 inverted 2 high	—	6 3 paradoxical 2 inverted 1 high	13	9	3
GROUP II ASHD HCVD (non-angina) (21 cases)	—	4	8	2 2 high	—	5 5 diphasic or inverted	7	10	1
GROUP III Miscellaneous (12 cases)	1	1	—	1 1 high	1 1 diphasic	—	3	3	1

* Inverted—from an upright to an inverted T wave.
High—from an upright to a high T wave.
Diphasic—from an upright to a diphasic T wave.
Paradoxic—from an inverted to an upright T wave.

S-T and T Changes

The incidence of the abnormal electrocardiographic changes observed in 54 patients is summarized in table 3.

Of 21 patients in group I, abnormal S-T depression was recorded only during exercise in five (figs. 3 and 4, S. G.), only during recovery in two and during both exercise and recovery in 10 (fig. 5). Four patients showed abnormalities in the T wave only during exercise: two with inversion of the T wave (fig. 4, M. T.) and another two with the development of high T waves (fig. 6). T-wave changes occurred during both exercise and recovery in six patients (figs. 2, 6). Ventricular premature beats occurred during exercise and recovery in

during exercise and five patients showed either an inverted or diphasic T wave during both exercise and recovery. Ventricular premature beats were registered during exercise and recovery in one patient.

In group III the incidence of S-T and T-wave abnormalities was low. One patient showed abnormal S-T depression and another high T waves only during exercise. The third patient had S-T depression and diphasic T waves only during early recovery.

Abnormalities of the S-T segment and T wave which developed during exercise usually persisted through the first three minutes of recovery and returned to the resting pattern by the eighth minute of recovery.

Elevation of the S-T segment occurred in one case during exercise and early recovery. The case is not included in this series. Pro-

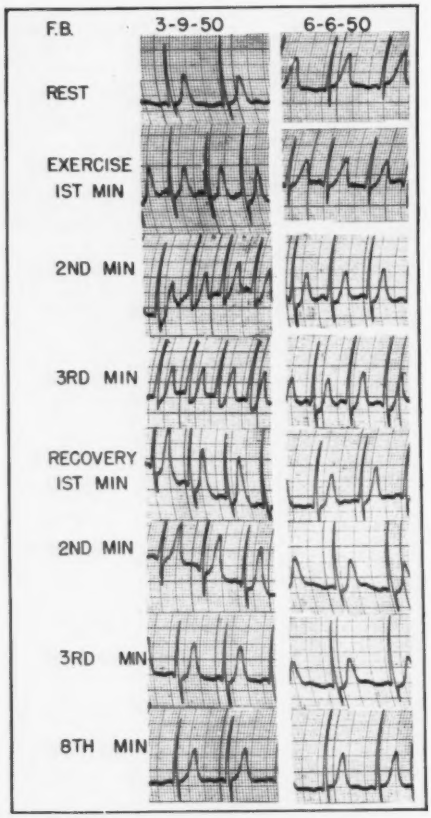

FIG. 3. *F. B.* A 37 year old man with history of angina pectoris. He did not complain of any precordial pain during both double two-step tests. Note marked S-T depression during exercise on 3/9/50 and less marked S-T depression during exercise on 6/6/50. In either instance the changes are not significant during recovery. This case illustrates three points: (1) No constant parallel exists between precordial pain and electrocardiographic abnormalities. (2) Changes indicative of coronary insufficiency may occur only *during* exercise and not after exercise. (3) Similar changes may be reproduced even after a period of three months.

longation of P-R interval or widening of QRS complex were not observed.

DISCUSSION

No previous study of electrocardiographic changes during the performance of Master's two-step test has been reported. Movements of the extremities preclude recording any satisfactory tracings during exercise by using Master's original method. With precordial

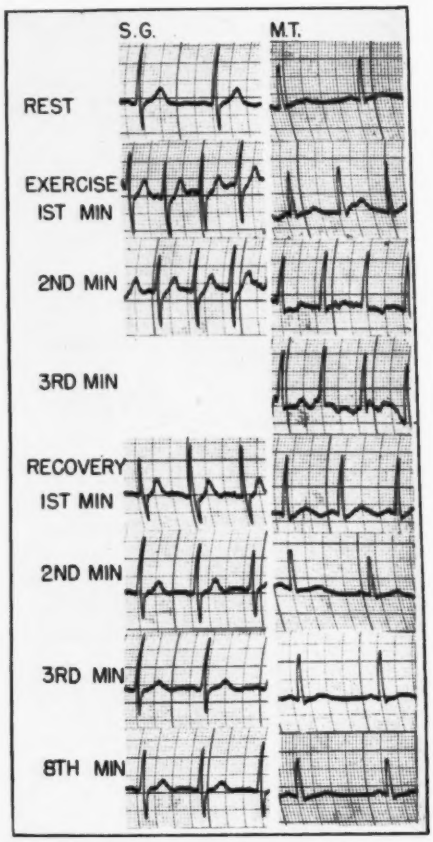

FIG. 4. *S. G.* A 59 year old man with history of angina pectoris and also evidence of anemia. He was unable to exercise for more than two minutes because of precordial pain and dyspnea. The electrocardiogram shows distinct S-T depression only *during* exercise and not after exercise. *M. T.* A 57 year old man who had had an attack of anterior myocardial infarction five years ago and since then frequently complained of precordial pain after exertion. The CB_4 lead shows a low T wave which becomes inverted only during the second and third minutes of exercise. Note the upright T wave in the recovery period.

lead (CB_4 or CB_5) it is possible to record the electrocardiogram during exercise without difficulty or interference. Most investigators agree that the precordial lead is more sensitive than any of the three standard limb leads.[4, 8–10]

This is understandable according to the principle that "regions close to the exploring electrode influence the pattern obtained to a greater degree than do areas remote from it."[11]

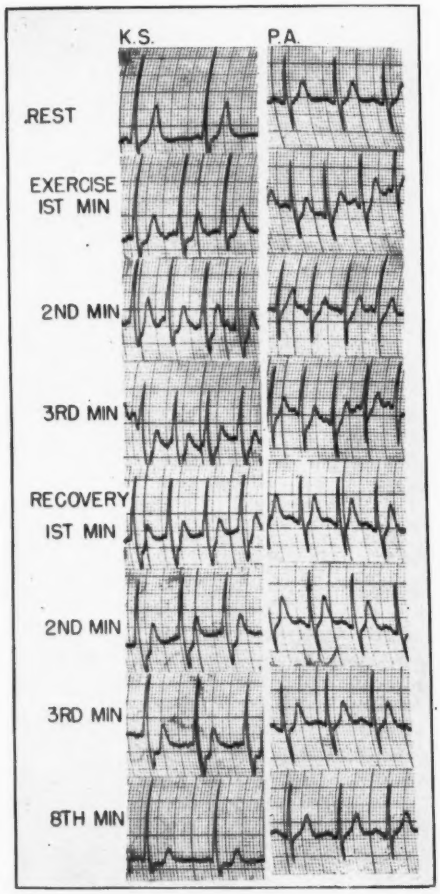

FIG. 5. *K. S.* A 39 year old man with typical history of angina pectoris. Patient died of an attack of acute myocardial infarction two weeks after this test was performed. *P. A.* A 56 year old man with typical history of angina pectoris.

The exercise electrocardiogram in these two cases shows marked depression of the S-T segment during both exercise and recovery. Note that the S-T depression actually occurs early in the first minute of exercise.

The potential of the right scapular region, on which the indifferent electrode is placed, varies through a relatively small range.[11]

Other investigators[4, 8, 12] have pointed out that the double two-step test demonstrates

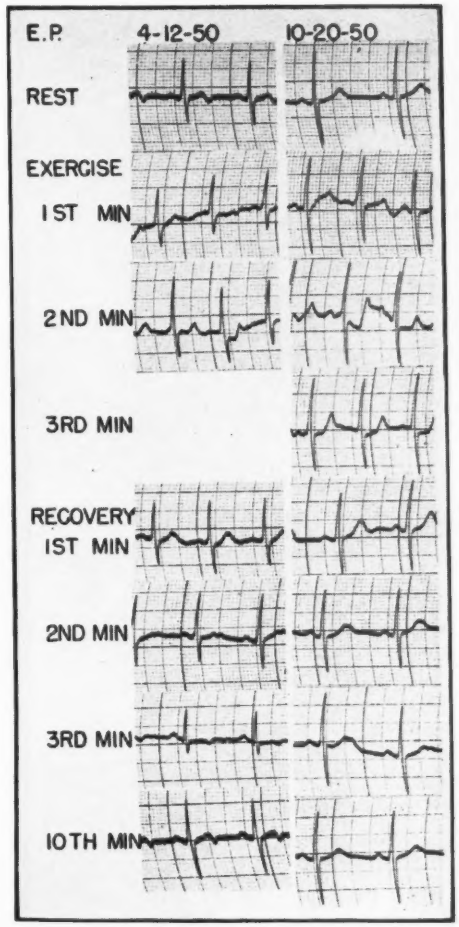

FIG. 6. *E. P.* A 59 year old man with typical history of angina pectoris. On 4/12/50 he was able to exercise for only two minutes because of dyspnea and precordial pain. The exercise electrocardiogram shows a so-called paradoxical response. The diphasic or inverted T wave at rest becomes upright during exercise and early recovery. After dietary management for a period of six months, his condition was improved and his precordial pain was less frequent. On 10/20/50 another exercise test was performed. This time he completed the double two-step test with only slight discomfort, and the resting electrocardiogram (lead CB_4) shows an upright T wave. During the second and third minutes of exercise, there is a distinct increase in the amplitude of the T wave associated with S-T depression. Both the paradoxic response and increase in the amplitude of T wave are the result of subendocardial ischemia.

abnormalities in many patients in whom the electrocardiogram is normal in the standard

test. For this reason, we used the double two-step test as standard procedure in our study. If severe symptoms develop or if marked abnormalities appear in the electrocardiogram the test may be interrupted immediately. Indeed, unlimited exertion in order to produce pain may be hazardous. In some cases electrocardiographic abnormalities may occur without symptoms, since no constant parallel exists between pain and electrocardiographic changes.[4, 13]

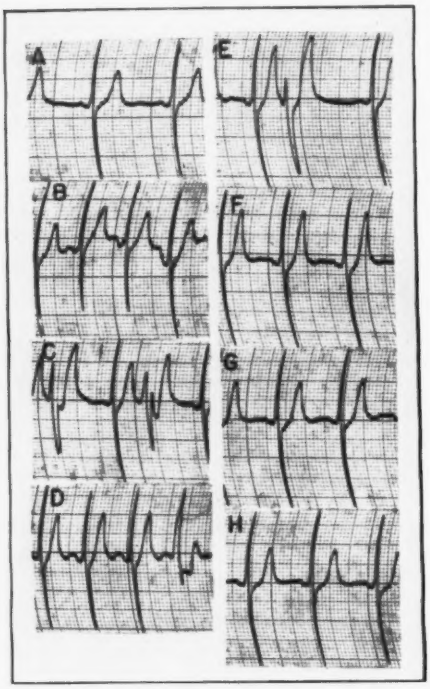

FIG. 7. The patient is a 52 year old woman who manifests classic symptoms of angina pectoris. Beginning in the recovery period the patient experienced somewhat marked though temporary symptoms, but note that an arrhythmia is recorded earlier than this in the second minute of exercise. *A*—Rest. *B*, *C* and D—Exercise. *E*, *F* and *G*—Early recovery. *H*—Late recovery.

Abnormal findings in the exercise electrocardiogram have been demonstrated in normal subjects under unusual stresses.[2] Therefore, we believe that any exercise for the diagnosis of coronary insufficiency should be standardized.

Changes of heart rate may be observed by taking electrocardiogram during the exercise period. The average heart rate during exercise was considerably higher in the patients than that in the normal subjects for the corresponding minute. Furthermore, the heart rate in at least one of the three minutes of exercise exceeded the maximum rate recorded in the normal subjects in 15 of the 54 patients.

Changes of the Q-T interval in normal subjects performing the double two-step test have been uniform and consistent. The Q-T/T-Q ratio during exercise was always less than 2.2 no matter what the heart rate. In some patients the ratio reached 4 or 5 and these values were associated with a very rapid heart rate. The Q-T/T-Q ratio is closely related to, but not entirely dependent upon, the heart rate. Therefore, both heart rate and Q-T/T-Q ratio may be a very useful index in determining myocardial function: The more rapid the rate, the higher the Q-T/T-Q ratio and the poorer the function.

The significance of changes in the $Q\text{-}T_e$ interval in patients with coronary insufficiency requires further study.

This study demonstrates that abnormal electrocardiographic changes such as S-T depression, alteration of the T wave and appearance of ventricular premature beats actually occurred *during* exercise and persisted to the recovery period in most cases. These changes are frequently diagnostic, and abnormalities occurring during exercise may be the only indication of coronary insufficiency. Our results show that false negative tests may be obtained in about 20 per cent of the cases of angina pectoris, if tracings are not made during exercise.

It should be noted, however, that electrocardiographic abnormalities indicating coronary insufficiency may be seen during and after exercise in patients without angina pectoris.[2]

Recent experimental and clinical studies[14–19] have shown that S-T depression in the precordial leads is due to injury in the subendocardial layer of myocardium. Inversion of an upright T wave in the precordial leads is probably due to a lesion of the epicardial surface, and reversion of an inverted or diphasic T

wave (paradoxical positive T wave change) in the same leads may be an indication of endocardial injury with "delayed repolarization." Experimental evidence also indicates that minor injury to the subendocardial myocardium may result in an increase in the amplitude of an upright T wave.[11, 20] We believe that the abnormal increase in the amplitude of an upright T wave during exercise is significant in human subjects. This change may be an indication of early subendocardial ischemia. An upright T wave in the precordial leads of some patients may increase in amplitude (suggesting subendocardial ischemia) earlier than or in association with the classic depression of the S-T segment indicating subendocardial injury due to coronary insufficiency.

Summary and Conclusion

1. A method for recording precordial electrocardiogram (CB_4 or CB_5) *during* exercise in performing Master's two-step test is described in detail. The electrocardiograms were recorded in four periods: (a) resting, (b) exercise, (c) early recovery, and (d) late recovery.

2. The double two-step test was performed in 32 normal subjects and 54 patients with various cardiovascular diseases. The changes in the electrocardiogram during and after exercise are reported and discussed.

3. The criteria for an abnormal response in the modified double two-step test are defined.

4. The significance of an increase in the amplitude of the T wave during exercise is clearly shown.

5. The modified method retains the merits of Master's original test and has several distinct advantages: (a) Changes in heart rate and the Q-T interval are recorded during exercise. The heart rate and the Q-T/T-Q ratio recorded during exercise may serve as a useful index of myocardial function. (b) It demonstrates that the electrocardiographic abnormalities in most cases of coronary insufficiency actually develop during exercise and persist to the recovery period. (c) In certain instances diagnostic changes are present only in the electrocardiograms taken during exercise, thus the sensitivity of the two-step test is augmented. (d) Since it makes possible electrocardiographic observation during exercise as well as during recovery it enhances the safety of the exercise test.

Acknowledgements

The authors wish to express their gratitude to Dr. William S. McCann, Professor of Medicine, University of Rochester School of Medicine and Dentistry, and to Dr. Jacob D. Goldstein, formerly Chief of Laboratories, the Genesee Hospital, for their continuous encouragement. The technical assistance of Miss Julia Nichols, Miss Carol Gouverneur, and Mr. S. T. Moore is acknowledged with thanks.

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Transient Ventricular Fibrillation

IV. The Effects of Procaine Amide on Patients with Transient Ventricular Fibrillation during Established Auriculoventricular Dissociation

By Sidney P. Schwartz, M.D., Leonard Hallinger, M.D., and Anthony Imperialli, M.D.

Procaine amide was given intravenously to three patients with transient ventricular fibrillation during established auriculoventricular dissociation at a time when they were free from symptoms as well as during the attacks. It was determined that this drug has a transitory slowing effect upon the auricles. It depresses rhythmicity in the auriculoventricular node, prolongs the refractory period of the ventricles, results in intraventricular conduction disturbance and the development of premature beats of the ventricles followed by the various forms of ventricular acceleration leading to ventricular fibrillation. Because of these alterations in heart rhythms, procaine amide is contraindicated in the treatment of such patients.

THE PURPOSE of this study was to determine the effects of procaine amide on patients with transient ventricular fibrillation during established auriculoventricular dissociation. It is apparent from various reports that this drug has been found useful in the abolition of various forms of premature beats of the ventricles and in the control of ventricular tachycardias.[1-4] More recent observations have revealed its beneficial effects on some of the supraventricular types of arrhythmias such as auricular fibrillation and nodal tachycardias.[5-6]

Mautz[7] was under the impression that when procaine was applied locally to the heart, it reduced cardiac irritability as indicated by the added intensity of stimulation necessary to induce premature beats of the ventricles or ventricular fibrillation. Other observers found it difficult to produce ventricular fibrillation by faradic stimulation after animals had received procaine.[8] Stutzman and his co-workers,[9] however, doubt the ability of procaine products to prevent adrenalin-induced ventricular fibrillation in dogs. Nevertheless, because of its beneficial action in some patients with ventricular tachycardia, it has been suggested that procaine amide would appear to be indicated in the various forms of ventricular acceleration and ventricular fibrillation that may form the basis of Adams-Stokes seizures during heart block.[10]

Yet, on the basis of experimental observations on the turtle heart and clinical experiences in a patient with auricular fibrillation who developed heart block and intraventricular conductions disturbance following procaine amide, Wedd and his co-workers[11] sound a warning that procaine amide may be particularly dangerous when there is disease of junctional tissues. With these points in view the following experiments were made.

Method of Study

Three patients who were subject to recurrent attacks of transient ventricular fibrillation during established A-V dissociation form the basis of this study. One of these has been under observation at the Montefiore Hospital for over 10 years and has been found to respond favorably to atropine sulfate.[12] Another male patient had his attacks for over two years and likewise responded to atropine sulfate. A third patient was seen at a time when he had numerous seizures of transient ventricular fibrillation and was given procaine amide for their relief.

The natural course of the development of their seizures and the successive alterations in the rhythm of their hearts leading to these attacks, as well as the changes following the revival of the heart from transient ventricular fibrillation were studied carefully prior to the experiments.

The patients were kept in the electrocardiographic circuit or under personal supervision throughout the

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entire day of the experiments so as to be certain of the nature of the cardiac mechanism present at any one time. Continuous electrocardiograms were obtained prior to, during and subsequent to the injection of the drug and whenever it was found of interest after that.

No other drugs were used for one week prior to the experiments except atropine sulfate as indicated in the specific protocols. We wished to determine the direct effects of procaine amide on the sinoauricular and auriculoventricular nodes in the absence of vagal influences.

These studies were concerned only with the intravenous effects of procaine amide. In many preliminary experiments, the minimal dosage of the drug sufficient to yield a response with changes in the rhythm of the heart during A-V dissociation was found to be 200 mg. diluted with 3 cc. of physiologic saline. This amount was given intravenously over a period of five minutes. For control purposes, similar amounts of physiologic saline were injected on the alternate days of the experiments.

In one instance, peripheral pressure changes were recorded with a manometer inserted in the left femoral artery and records were obtained simultaneously with the electrocardiograms, prior to, during and subsequent to the injection of procaine amide.

The changes which were induced by procaine amide may be best exemplified by a description of the following experiments each one of which depicts a particular action of the drug.

Results of Experiments

In one patient, the intravenous injection of procaine amide in doses of 200 mg. each, yielded no changes on three separate occasions. In the fourth experiment, there developed short runs of bigeminal rhythm due to alternate premature beats of the ventricle, that lasted for 37 minutes after the injection. However, since he had shown such premature beats on the morning of this day, it was likely that their appearance was fortuitous and not the result of the drug.

In another patient the sequence of events was of unusual interest. On one occasion the basic ventricular rate averaged 34 beats per minute and the auricular rate 107 beats. The rhythm was regular. Immediately following the injection of 200 mg. of procaine amide diluted with 3 cc. of distilled water within five minutes, and before the needle was out of the vein, the ventricles slowed to 25 beats per minute and the auricles to 83.6 beats (fig. 1*A*–1). In less than a few seconds there appeared premature beats of the ventricles at first singly (fig. 1*A*–2) and then in groups of two (fig. 1*A*–3). The returning cycle following these premature beats was of the same duration as the cycles of the basic ventricular complexes, which were downwardly directed and were of the same shape, size and form from beat to beat. The T waves accompanying these were likewise directed downwardly.

Thirty seconds after the end of the injection, there was a sudden stoppage of ventricular activity lasting about six seconds (fig. 1*B*–1) before the basic ventricular rhythm returned. Now the T waves of the ventricular complexes were large and negative with a prolonged RS-T segment and they presented on their ascending limbs, portions of premature beats of the ventricles resulting in the development of so called "deformed ventricular complexes." Such abnormalities in the ventricular complexes have been previously described as important preliminary events in the onset of ventricular fibrillation during established A-V dissociation.[13]

Now, the returning cycles following the premature beats of the ventricles increased progressively (fig. 1*B*-2, 3 and 4, 5) averaging 6.4 to 8.4 seconds in duration whereas usually they were only 2.0 seconds. For the next half minute, the patient became pale, perspired profusely, shut his eyes momentarily and could not respond to questions. No heart sounds were audible and no pulses were palpable during this episode.

In the next 15 seconds he became rigid and had a slight convulsive seizure. Apnea with cyanosis supervened and the cardiac mechanism registered for the next 27 seconds was one of ventricular fibrillation ended by a premature beat of the ventricles. This was followed by ventricular standstill of seven seconds duration with persistant auricular activity and then the return of a basic ventricular beat (fig. 1*C*).

Ten minutes after the injection, the respirations which were of the Cheyne-Stokes variety returned to normal and the basic ventricular rhythm was restored. The idioventricular rate however, waxed and waned for a time with an

average ventricular rate varying between 20.2 and 31.2 beats per minute (fig. 1*D*), finally returning to its basic normal, 14 minutes after the injection.

On another occasion, in the same patient, the basic ventricular rate averaged 31.2 beats per minute and the rhythm was regular without the interposition of any premature beats of the ventricles (fig. 2*A*–1). For the previous seven days the patient had received intramuscular injections of atropine sulfate (2.0 mg.) each day so as to regularize his cardiac mechanism and prevent a fluctuation in the rate of the idioventricular pacemaker.

Immediately following the injection of 200 mg. of procaine amide diluted with 3 cc. of saline, there ensued a standstill of the ventricles of 7.52 seconds duration with 13 auricular beats being present to each ventricular contraction (fig. 2*A*–2).

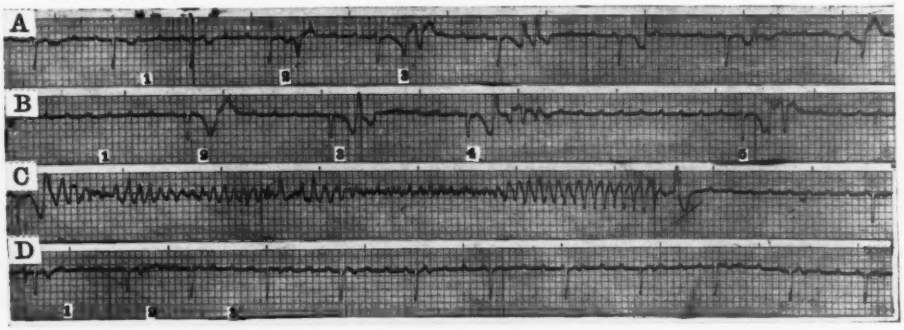

FIG. 1. *A*. Procaine amide results in the appearance of premature beats of ventricles immediately after injection. *B*. Thirty seconds later. (1) Standstill of ventricles. (2, 3, 4) Increase in duration of returning cycles following premature beats. *C*. Ninety seconds later. Ventricular fibrillation followed by prolonged standstill of ventricles. *D*. Return of basic rhythm with irregular ventricular cycles, 10 minutes after injection.

Heavy vertical time lines = 0.20 second.

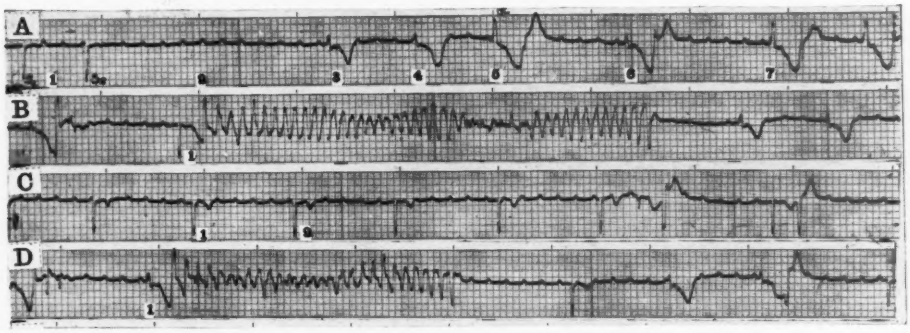

FIG. 2. *A*. (1) Control record showing basic rhythm in atropinized patient. (2) Procaine amide causes standstill of ventricles immediately after injection. (3) Change in pacemaker from A-V node to bundle. (5, 6, 7) Deformed ventricular complexes and increase in the duration of returning cycles of premature beats. *B*. Fifteen seconds later. Ventricular fibrillation. *C*, *D*. Alternating periods of premature beats with long returning cycles and ventricular fibrillation.

Following this period of standstill, the pacemaker of the ventricles was assumed by another focus either in the A-V node itself or one of its bundles as may be judged by the presence of upwardly directed ventricular complexes accompanied by large negative T wave and a prolonged RS-T segment (fig. 2*A*–3). The T waves accompanying this new ventricu-

lar complex became progressively deeper from beat to beat (fig. 2*A*–3, 4, 5). Soon this deformity was enhanced by the superposition of fractions of premature beats of the ventricles on the ascending limbs of the T waves, forming bizarre deflections. These "deformed ventricular complexes" are identical to those previously described as premonitory to the abrupt onset of ventricular fibrillation.

The returning cycles following the premature beats of the ventricles increased in duration very early (fig. 2*A*–5, 6 and 6, 7).

(fig. 2*C*–1) by another period ventricular fibrillation of 8.6 seconds duration (fig. 2*D*–1). Premature beats of the ventricles and "deformed ventricular complexes" alternated for two and one-half minutes when the patient suddenly lost consciousness. He became very pale, apnea was followed by intense cyanosis lasting about 20 seconds. There was a drop in blood pressure and pulsations were absent at the radial artery. No heart sounds were audible at the apical region of the heart. The return of the basic rhythm was heralded abruptly by a sudden

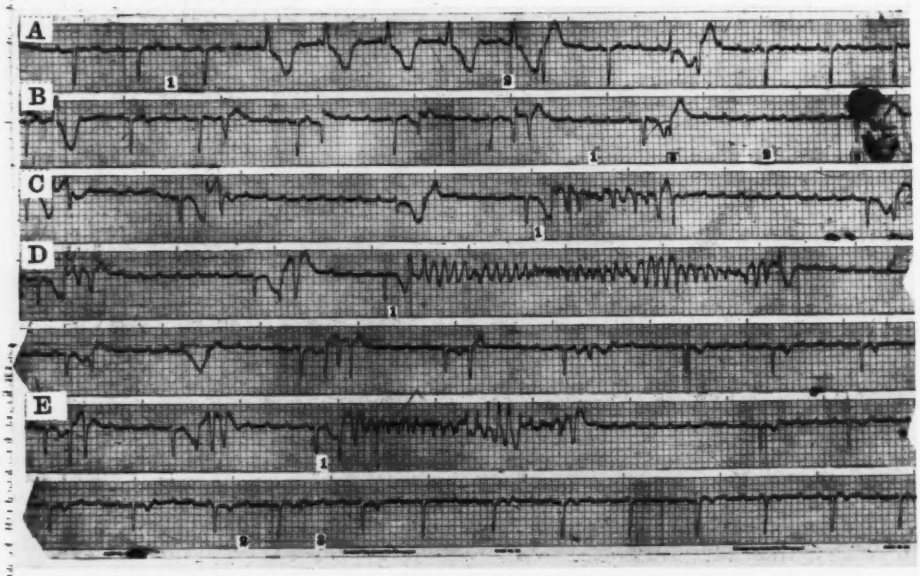

FIG. 3. *A*. In control record normal ventricular complexes alternate with aberrant deflections. *B*. (1, 2) Procaine amide causes abrupt increase in returning ventricular cycles following premature beats. *C*, *D*. Alternate periods of standstill and ventricular fibrillation with final return to basic rhythm, five minutes after injection.

Fifteen seconds after the injection, the direction and form of the ventricular complexes changed abruptly and after a series of alternate premature beats of the ventricles had disrupted the basic rhythm, there was ushered in a period ventricular fibrillation lasting 14.4 seconds (fig. 2*B*–1) . A pause of 2.6 seconds ended this period and the idioventricular pacemaker reasserted itself.

For the next 20 seconds, the basic ventricular rate slowed to 20 beats per minute and the rhythm was regular only to be interrupted

flush of the face but the speech remained incoherent for some time thereafter.

From then on, for the next four hours, his rhythm was that of short runs of ventricular fibrillation alternating with a bigeminal rhythm as a result of the persistent presence of premature beats of the ventricles during established A-V dissociation. All of these abnormalities disappeared by the next morning.

In a third experiment procaine amide was given to a patient at a time when the idioventricular rhythm was labile (fig. 3*A*–1). It

consisted of downwardly directed ventricular complexes with upwardly directed T waves, and with a cycle measuring 2.08 seconds in duration. This rhythm alternated with one consisting of aberrant ventricular complexes with downwardly directed large T waves and a slower cycle of 1.84 seconds duration (fig. 3*A*–2)

Three seconds after the injection of the drug, there was an abrupt increase in the duration of the returning cycle following the premature beat of the ventricles (fig. 3*B*–1) from 2.08 seconds to 3.60 seconds. Each succeeding returning cycle following a premature beat of the ventricles became progressively longer (fig. 3*B*–2) and varied between 5.8 seconds and 6.4 seconds in duration. At such times, the patient became pale, perspired profusely and shut his eyes momentarily. He complained of nausea and pain in the chest.

Three minutes after the injection, when the basic heart rate averaged only 10 beats per minute as a result of depression of impulse formation in the A-V node, there appeared markedly negative T waves. Deformed ventricular complexes now resulted from the superposition of fractions of premature beats of the ventricles on the ascending limbs of the T waves. In less than a few seconds after their appearance, there developed a short run of ventricular fibrillation of 4.0 seconds duration followed by a standstill of the ventricles of 6.0 seconds duration (fig. 3*C*–1).

For the next minute (fig. 3*D*–1) longer periods of ventricular fibrillation were followed by periods of standstill of the ventricles, so that no heart sounds were audible and no pulses would be felt for 18 seconds at a time. With this episode, the patient lost consciousness and had a short convulsive seizure. After two and one-half minutes of recurrent periods of ventricular fibrillation and standstill of the ventricles (fig. 3*E*–1) there was an abrupt return to the basic cardiac mechanism five and three-fourths minutes after the injection.

The return of the basic rhythm was associated with a waxing and waning of the impulse pacemaker in the A-V node so that the ventricular cycles were at times shorter (fig. 3*E*–2) and at times longer (fig. 3*E*–3) until a uniform cycle prevailed for the rest of the day, four and one-half hours after the beginning of the experiment.

Procaine amide was given to two patients at a time when they were both experiencing recurrent Adams-Stokes seizures due to long periods of ventricular fibrillation in the preceding 24 hours. In both instances, immediately after the injection, the seizures increased in duration and persistence. One patient died 24 hours after the injection without regaining consciousness following one such long seizure. The other, after repeated attacks of all forms of ventricular acceleration and ventricular standstill, remained cyanotic with irregular breathing and in a semistuperous state for the next five days. The attacks subsided gradually after he had been using oxygen to overcome the profound anoxemia present continuously during that period.

Discussion

These observations reveal that in patients with transient ventricular fibrillation during established A-V dissociation, the action of procaine amide may differ from day to day in the same patient and may act variably in different patients. It has been noted that the A-V pacemaker of the heart may at times be in a "labile" state when it responds to drugs very readily with a change in the rate and rhythm of the ventricles and at other times it may remain in a relatively "fixed" state when it may not respond at all. This is very likely in part due to the state of the extrinsic nervous mechanism of the heart and in part to physicochemical factors inherent in the A-V pacemaker itself.

The sinoauricular pacemaker of the heart which is usually under nervous influences may be depressed very early after the use of procaine amide. Such transitory slowing in well atropinized patients with A-V dissociation must then be considered to be the result of the direct depressing effect of the drug upon the sinoauricular node itself.

Of greater clinical significance was the early and marked depressing effects of procaine amide upon the A-V pacemaker itself. This specialized junctional tissue may be so sensitive that it responds with long pauses of ventricular in-

activity with impulse formation in the A-V node displaced to another part of the heart, such as in one of the bundles or the ventricles themselves. This is reflected in the electrocardiogram by an aberrant ventricular complex different from that present usually and with a change in rhythm. It would appear that conduction within the ventricles themselves is likewise disturbed at the same time that the A-V pacemaker is affected.

Another index of the depressing action of procaine amide on the ventricles may be gained from the constant changes noted in the prolongation of the returning cycles following the presence of premature beats of the ventricles after these have appeared.

Usually the returning cycles of the premature beats of the ventricles during A-V dissociation are approximately the same length as the cycles of the idioventricular rhythm of the heart. Indeed sometimes the returning cycles are shorter. However, if repeated attacks of ventricular fibrillation recur with increasing frequency, the duration of the returning cycles in the presence of premature beats of the ventricles may be prolonged.

It is important to bear this in mind when studying the effects of drugs in such patients with heart block. If any depression of rhythmicity or conduction takes place, this portion of the heart cycle may be the earliest to show changes.

Again, in studying the mode of revival of the heart from ventricular fibrillation, it was pointed out that shorter runs may be ended abruptly either by a premature beat of the ventricles or by the last of the fibrillary waves. A postundulatory pause follows with the return of the basic rhythm immediately after. The longer runs of ventricular fibrillation may end in a period of standstill of the ventricles while the auricles continue their contractions.[14]

This postfibrillary standstill of the ventricles was found to be longest in duration when the heart had been the seat of repeated bouts of ventricular fibrillation, recurrent short fibrillary periods or even numerous premature beats of the ventricles. The prolongation of ventricular inactivity after the cessation of ventricular fibrillation appeared to be dependent more on these factors than on the duration of any one attack of fibrillation itself.

For example, fibrillary periods lasting one and one-half minutes appearing early in the course of the syndrome would return to a basic rhythm of A-V dissociation without the intervening periods of standstill of the ventricles. On the other hand, shorter periods of fibrillation lasting only a few seconds have been known to be followed by a prolonged period of standstill after the presence of numerous attacks of ventricular fibrillation or prefibrillary periods preceding them.

Cushny[16] noted that when the ventricle was beating automatically and its usual slow rhythm was accelerated by a series of shocks at a more rapid rate, it did not resume its original rhythm when the artificial stimulus was withdrawn. As a general rule the ventricles remained quiescent for some time and then recommenced beating very slowly and irregularly, accelerating their rhythm until they resumed their original rate before stimulation.

The factors determining the appearance of these pauses were attributed in part to the duration of stimulation but primarily to fatigue increasing for some time after the acceleration had ceased.

This type of retarded rhythmicity following rapid beating of the dissociated ventricles has its counterpart in the postfibrillary periods of the human heart in patients with transient ventricular fibrillation during established A-V dissociation. By *prolonging this period* in further depressing its action, procaine amide retards rhythmicity in the A-V node.

These transitory but profound changes in the depression of rhythmicity in the A-V node and conduction disturbances within the ventricles would in themselves be of little importance in such patients were it not for the fact that simultaneously with their appearance, there may arise from the ventricles multiple ectopic foci, which always appear after the basic ventricular deflections.

The ease with which premature beats of the ventricles and the various forms of ventricular acceleration develop during heart block, more than with any other abnormal cardiac mechanism, is well known. The possibility sug-

gests itself that in certain patients with A-V dissociation stimuli formation in ectopic foci of the ventricles is conditioned by the state of the A-V pacemaker of the heart. It has been repeatedly observed that variations in the rate and rhythm of the A-V pacemaker invariably precede the development of premature beats of the ventricles in such patients even though they may last only a few seconds at a time. Since these premature beats of the ventricles are a necessary preliminary event in the development of transient ventricular fibrillation, such a drug as procaine amide which provokes their appearance is distinctly contraindicated in them. No changes in blood pressure were observed to have followed the use of procaine amide in any of the patients during the presence of A-V dissociation when the basic rhythm was present either before or after the development of transient ventricular arrhythmias. Pressure changes however were found to be associated with the abnormal rhythms themselves.

Conclusions

A study was made of the effects of procaine amide on three patients with transient ventricular fibrillation during established A-V dissociation.

It was determined that the action of this drug is variable from patient to patient, and in the same patient it differs in its effects from day to day.

Procaine amide was found to have an early transitory depressing effect upon the sinoauricular node since it slowed the auricular rate even in the well atropinized patient.

Procaine amide depressed impulse formation in the A-V node as evidenced by (a) temporary cessation of ventricular activity with a profound slowing of the heart rate during already existing heart block, (b) increase in duration of returning cycles following the appearance of premature beats of the ventricles, (c) undue prolongation of ventricular standstill in the presence of persistent auricular activity following revival of the heart from ventricular fibrillation, (d) displacement of the A-V pacemaker to a lower portion in the ventricles such as in one of the bundles as evidenced by the appearance of new ventricular complexes different in shape, size and form from those present before the use of the drug, and finally (e) by a waxing and waning of rhythmicity in the A-V node when the effects of the drug began to wear off as may be judged by the variability in the rate and rhythm of the heart from moment to moment with the return of the basic complexes.

This action of procaine amide on the junctional tissues was independent of the influence of the nervous mechanism on the A-V node in these patients.

Procaine amide depressed conduction within the ventricles as evidenced by (a) a change in the shape, size and form of the ventricular complexes to one with marked aberration previously not present, (b) unusual prolongation of the RS-T or Q-T segments and (c) the appearance of large negative T waves. These changes favored the development of deformed ventricular complexes similar to those observed to be the forerunner of ventricular fibrillation in the natural course of this syndrome during heart block.

Procaine amide favored the development of ectopic beats of the ventricles resulting in the various forms of ventricular acceleration ending in transient seizures of ventricular fibrillation. All of these changes appeared much earlier and lasted longer when procaine amide was given in the presence of intraventricular conduction disturbance, premature beats of the ventricles or when recurring seizures of ventricular fibrillation were present.

It was found that the effects of procaine amide in such patients appeared and disappeared earlier than the effects of quinidine when administered under similar conditions.

Procaine amide is contraindicated in patients with the various forms of ventricular acceleration leading to ventricular fibrillation during established A-V dissociation.

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The Distribution of Cardiac Potentials Around the Chest in One Hundred and Three Normal Men

By ERNST SIMONSON, M.D.

Chest leads farther right to V_1 and farther left to V_6 have been suggested, and are increasingly used, for diagnosis of right ventricular or posterior wall lesions. Normal standards are provided for the regional distribution of seven arbitrarily defined patterns and amplitudes of main deflections, in five positional groups, in 15 leads around the chest, resulting in statistical evaluation of 600 electrocardiographic items. In general, the results favor a much more conservative interpretation than has been noted in the past. Some implications to electrocardiographic theory are discussed.

ALTHOUGH MULTIPLE precordial leads have been generally introduced in clinical routine electrocardiography, a normal sample adequate in size for normal standards of the leads V_1 to V_6 has not been available until very recently (Sokolow and Friedlander[1]). For many years Kossmann and Johnston's[2] material of only 30 normal subjects was used as a normal reference.[3] In the series of 52 cases of Myers and co-workers[4] the normality of the heart was shown by autopsy, but no statistical analysis was made; the presentation of their material was of a descriptive character. Even Sokolow and Friedlander's larger sample is not satisfactory because of the heterogeneous character of their group and the failure to differentiate between the electrical heart positions. Dolgin and associates[5] investigated the differences between CR, CL, CF and V leads, but the samples were too small to be used for the calculation of normal standards.

It has been recognized that in conditions of pronounced clockwise or counterclockwise rotation around the long axis, the six conventional precordial leads V_1 to V_6 are not sufficient to arrive at a definite interpretation. Right lateral leads have been suggested for suspected right ventricular preponderance[6–9] and V_7, V_8 or other left back leads for suspected coronary insufficiency or infarct of the posterior wall.[10,11] In the absence of normal-standard material, the standards for other leads, such as V_1 or V_R for the right lateral leads, and V_6, V_L or V_F for the back leads, are used currently as criteria of normality.

In this paper information is provided on the distribution of electrocardiographic patterns around the chest at the level of the heart in 103 normal men. These should have immediate value as a background for clinical interpretation but the results also have a bearing on some theoretic aspects of unipolar electrocardiography.

METHOD

Fifteen leads were taken around the chest at the level of the heart, in addition to the three standard and three unipolar limb leads. Since this work was done with the view of application to clinical electrocardiography, the conventional precordial leads were taken in the supine position, following the customary routine. The back leads were taken in the sitting position. In control experiments on 23 normal men it was shown[12] that the change of the body position from supine to sitting produces only minor changes in the precordial electrocardiogram, which were found in all but one item (R wave in V_2) to be statistically not significantly different from zero. The change of body position, therefore, would not produce any appreciable error in the statistical analysis of amplitudes or pattern distribution.

For analysis of the distribution of electrocardiographic patterns, the leads were expressed in terms of angles (degrees) from a hypothetic center in the heart. The center was obtained from frontal chest plates in the following way: (1) one half of the long diameter, measured from the junction of the right

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atrium shadow with the aortic shadow to the most distant apical point, (2) arbitrary estimate of a central point.

The two approximations agreed very closely, the measured point tending to fall slightly below the estimated. At the level of the center, the transversal diameter was measured, and the position of the reference point (fig. 1). Each lead is expressed both in the conventional way and in terms of an angle. The 0°–180° line was arbitrarily chosen as the transversal line through the center, with the increase of the angle in clockwise rotation. Using this procedure, the location as well as the extent of the various patterns could be given in terms of the mid-

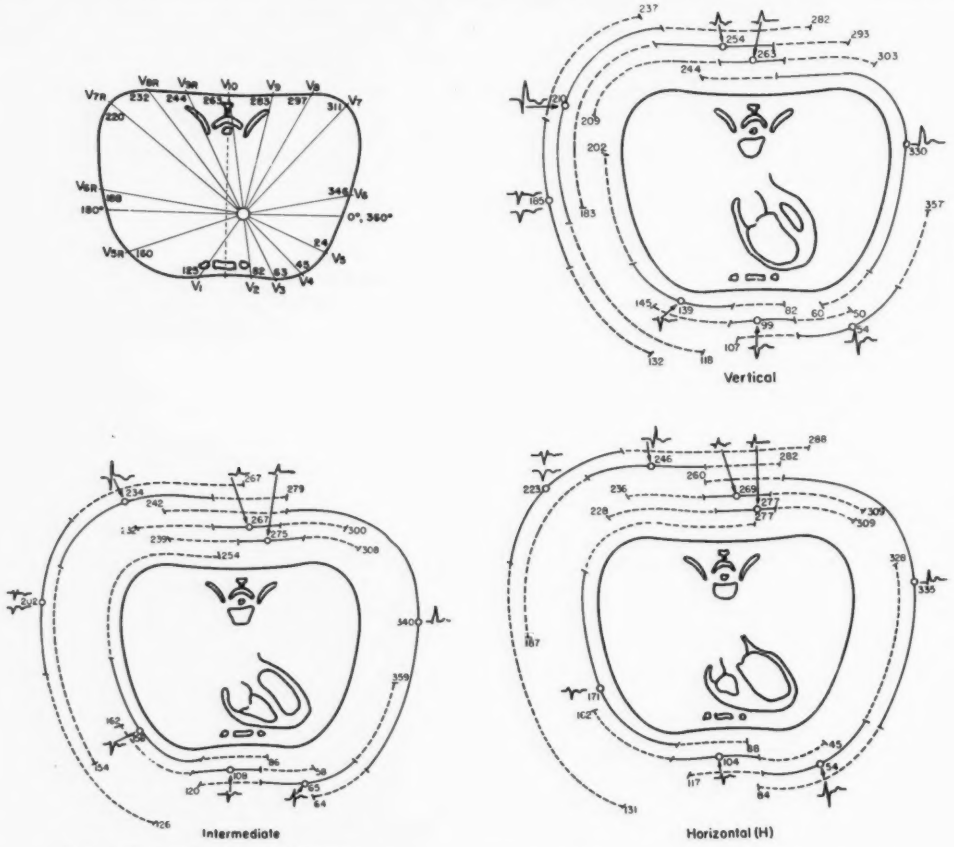

FIG. 1. Upper left hand diagram:

Cross section of chest with lead positions, expressed as V leads and in degrees of angle with a hypothetic center (circle) in the heart. The transversal 0°–180° line through the center follows Bayley's[26] triaxial reference system of the frontal plane, but does not correspond to any actual lead.

Other three diagrams: Distribution of patterns in three heart positions. The circles are the average midpoints; the small vertical lines connected through a solid line denote the mean upper and lower endpoints, and the broken lines show the upper and lower limits for 95 per cent of normal population.

center expressed in per cent of this diameter, with the zero point on the right side.

The center (57.6 per cent of the transversal chest diameter), as shown in figure 1, is the average of 70 values. The interindividual variability was surprisingly small, the extremes being 61 and 52.5 per cent. This center, therefore, seemed to be a suitable point (MP) and two endpoints (U and L), as degrees or arc equivalents. The endpoints of a given pattern were taken as the arithmetic means between two successive leads with different patterns, and the midpoint (MP) was calculated as the arithmetic mean between the two endpoints.

As an example, assume that one pattern (A)

extends from V_3 (=63°) to V_4 (=45°), and another pattern (B) from V_5 (=24°) to V_8 (=297°). The endpoints U and L for pattern A are then 73° and 35°, and for pattern B 35° and 290°. The midpoints would be $\frac{73+35}{2} = 54°$ and $\frac{290+395}{2} = 343°$, respectively, and the range $73 - 35 = 38°$ for A and $395 - 290 = 105°$ for B. This procedure made a statistical evaluation of the pattern distribution possible. The sagittal midline (broken line, fig. 1) and the transversal (0°–180°) line are given for orientation, although they do not correspond to any particular lead.

The outline of the chest was taken from an anatomic atlas[13] representing a cross section at the fifth intercostal level.

The geometric distribution of the following patterns was analyzed:

(1) rS, T−;
(2) rS, T+;
(3) qR, T+; (q up to 33 per cent of R).
(4) QR, T−; Qr, T−.

Transitional potentials were defined:

between (1) and (2): appearance of isoelectric or diphasic T,

between (2) and (3): RS; T+ or appearance of small polyphasic potentials,

between (3) and (4): qR with isoelectric, diphasic, or negative T.

In addition to the analysis of pattern distribution, the magnitudes of the QRS and T deflections were analyzed in each of the 15 chest leads. The means, standard deviations and limits for 95 per cent of the normal population were calculated for the distribution of patterns as well as for the amplitudes.

The electrocardiograms were classified in five positional groups (vertical "V," semivertical "SV," intermediate "I," semihorizontal "SH," and horizontal "H") using criteria of Wilson and associates[3] and Myers and Klein.[14]

The subjects were 103 men between 45 and 55 years of age. Careful clinical and laboratory examinations, including various stress tolerance tests, as well as the history, failed to show any evidence of clinical abnormality. All subjects had been examined annually for three years in this laboratory, so that probably this group was more highly selected in regard to absence of clinical abnormality than normal control groups usually would be.

The distribution of electrical positions in our group does not represent a random sample; the 103 subjects discussed here were selected from a larger group in order to obtain a representative number of individuals in each positional group. The number of subjects in the positional subgroups were: 23 in V, 14 in SV, 33 in I, 11 in SH, and 22 in H.

Results

Pattern Distribution

A graphic presentation of the pattern distribution in three different electrical heart positions is shown in figure 1. The outlines of the heart and its geometric position are, of course, only an approximation.

The regions over which the indicated patterns extend are shown as lines around the thorax, the small circles giving the position of the means for the midpoints and the solid lines the means of the endpoints for these patterns. The broken lines show the extremes for these patterns which may be expected in 95 per cent of "normal" men. These latter limits, calculated from the standard deviations, afford a basis for the differentiation between "normality" and "abnormality" in routine clinical interpretation.

No differentiation was made between the right lateral QS, T− pattern and rSr′, T− pattern, because they were found in the same location and because the differentiation becomes highly arbitrary in case of microscopically small r and r′. It was assumed, therefore, that both patterns are identical.

Analysis of figure 1 reveals:

1. There is a continuous transition from one pattern to the next, so that the precise differentiation between patterns is arbitrary;

2. there is considerable overlapping of pattern distribution;

3. mirror-patterns are found at opposite ends of projections through the heart;

4. the extent of most patterns is very wide and difficult to relate consistently to specific parts of the heart surface;

5. there are important differences of the pattern distribution, especially in the back and right lateral leads, in the five different electrical heart positions.

The continuous trends were true for each segment of the pattern, but there was considerable interindividual variability, even greater than can be seen in figure 1 which shows only the variability of the endpoints for each pattern. It is well known, from experience with the precordial leads V_1 through V_6, that

in normal persons a small Q wave may appear in V_3, associated with a transitional RS complex, or may not be seen in V_6 with a monophasic R or an RS complex. A similar situation in regard to other segments obtains in other regions which are less explored. For instance, the so-called left ventricular epicardial pattern, qR, T+, with its average midpoint around 340°, changes in the direction to the midline of the back in three ways: the R wave decreases, Q increases and T becomes isoelectric or inverted when the R wave is still relatively large, with a prominent Q wave, simulating the pattern of coronary insufficiency or posterior-lateral infarct in the regions V_7 to V_9. In regions V_7 and V_8, the electrode still faces the left ventricular wall.

difference between the endpoints in each individual and calculated from the S.D., give more precise information (table 1). Even so, the upper range limits, especially for the rS, T− (or rSr′, T−) pattern and the qR, T+ pattern are very wide. The narrow low range limits are also of interest. They are so small in several patterns (for instance rS, T− or QR, T−) that they may be missed entirely at the usual electrode distance.

The question may arise whether the arbitrary determination of angles and the hypothetic center in the heart might be a contributing factor to the large variability of pattern distribution and range. The arbitrary choice of the zero point is irrelevant for the validity of our procedure, but an incorrect position of the

TABLE 1.—*Upper and Lower Limits (95 Per Cent of the Normal Populatiin) for the Range (Arc Equivalents in Degrees) of Electrocardiographic Patterns*

Pattern	Vertical		Semivertical		Intermediate		Semihorizontal		Horizontal	
	High	Low	High	Low	High	Low	High	Low	High	Low
rS (r′) T−	95.0	2.0	121.1	0.0	118.6	8.8	113.1	0.0	150.6	15.6
rS T+	55.8	12.8	101.1	2.3	52.5	2.7	79.6	0.0	92.1	0.0
RS T+	86.7	11.9	83.3	12.5	84.9	14.5	94.8	9.6	93.6	16.0
qR T+	158.0	75.4	152.0	64.2	159.9	78.5	137.6	62.0	153.9	49.7
qR T_0	46.9	0.0	38.6	3.6	40.2	2.8	27.8	5.2	35.4	8.8
qR T−	77.6	0.0	48.7	0.0	46.3	2.5	45.5	3.9	40.5	4.7
QR (r) T−	119.1	2.7	86.8	0.0	96.0	0.0	98.6	6.2	59.6	0.0
QS T− (rSr′) T−	62.3	11.5	59.6	23.6	75.0	3.8	120.3	1.5	93.8	0.0

Although the continuity of trends makes the differentiation and definition of patterns arbitrary, they prove, at the same time, the general validity of our procedure of evaluation. Any other definition of patterns would have resulted in similar distribution diagrams, rotated clockwise or counterclockwise with reference to the diagrams in figure 1, according to the arbitrarily defined pattern limits.

The broken lines in figure 1 include the region where a given pattern may be found in 95 per cent of normal population, but the individual range for any pattern is exaggerated. The limits were obtained from the standard deviations of the endpoints; it is highly unlikely that any individual would be extreme both in the upper and lower endpoint. The upper and lower limits for the range of the pattern, defined as the

center for a given individual would change the projection of patterns onto the lead locations. However, this error was probably small. A difference of a few centimeters in the location of the center would not greatly change the situation, and the variability of the location of the center was comparatively small. The uncertainty of the correct position of the center does not limit the usefulness or applicability of the normal limits of pattern distribution and range, as presented in figure 1 and table 1. The situation is the same for any patient to whom the standards are applied as for any individual of our group in whom the standards were obtained. The only pattern where information about location and range is available is the "transitional" RS, T+ pattern, because its limits are included within the routinely taken

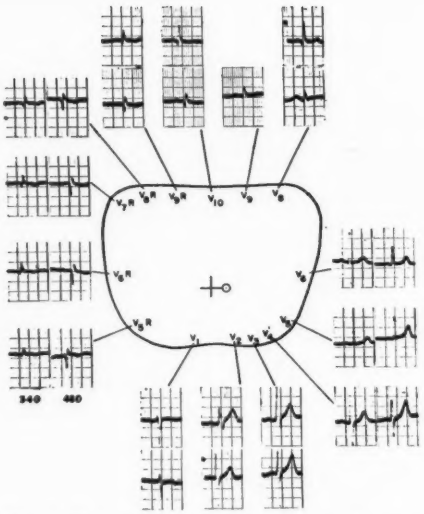

FIG. 2. Two cases (case 340: outer circle; case 460: inner circle) with pronounced "clockwise" rotation. The qR, T− pattern (340) and Qr, T− pattern (460) extends far to the right.

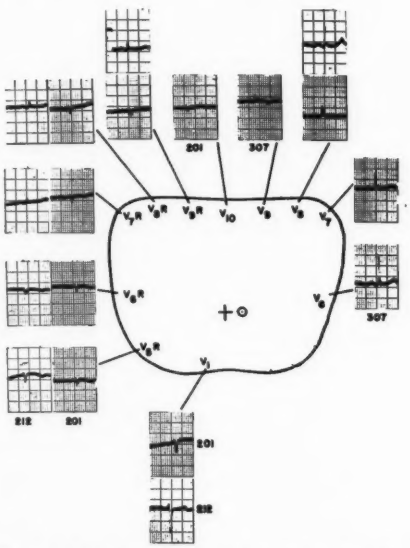

FIG. 3. Case 307, inner circle, V_6 to V_9: qR, T− pattern in V_8. Case 212, outer circle, V_8 to V_{5R}: qR, T+ pattern extends to V_{7R}. Case 201, inner circle, V_{10} to V_{5R}: wide range of rS, T− pattern.

precordial leads V_1 through V_6. Our range limits agree with the available information[4].

The upper and lower range limits of pattern distribution (fig. 1, table 1) are difficult to explain on the basis of the theory that the chest leads represent projections of local patterns from specific parts of the heart. The limits are, of course, not a result of calculations, but can be found in actual tracings. For example, figure 2 shows two examples of extreme "clockwise" rotation around the long axis of the heart, so that the essentially monophasic R, T+ pattern appears in V_5. The QR, T− pattern extends from V_{8R} to V_{5R} in case 460 (inner circle) and the qR, T− pattern from

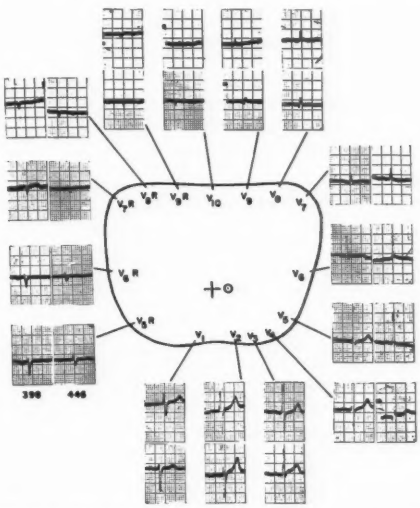

FIG. 4. Two cases (case 398: outer circle; case 446: inner circle) with wide range of isoelectric T in the left back leads.

V_{9R} to V_{5R} in case 340 (outer circle) simulating right ventricular preponderance.

Figure 3 shows the pattern distribution of three subjects: Case 307 from V_6 to V_9, inner circle; case 212 from V_8 to V_1, outer circle; and case 201 from V_{10} to V_1, inner circle. In case 307 the T− inversion appears already in V_8, simulating a coronary insuffiency pattern (qR, T−). In case 212 the qR, T+ pattern extends far to the right (V_{7R}); certainly, it would be impossible to relate this pattern at this location to left epicardial potentials. Case 201 demonstrates a wide range of the rS, T− pattern, extending from V_1 to V_{8R} (equivalent of 107°). In the two cases illustrated in figure 4 (case

398: outer circle; case 446: inner circle), the T− waves become isoelectric when R is still relatively high (V_7 in case 446; V_5 in case 398), and the range of the isoelectric T extends in both cases to V_9.

The effect of heart position, defined as rotation around an anteroposterior axis, on the horizontal pattern distribution is revealed by inspection of figure 1, but such comparison does not afford convenient visualization, and also lacks quantitative characterization. Figure 5 shows more directly the distribution of the QR or qR pattern, and their mirror pattern (RS or rS) in the back and right lateral leads V_8 to V_{5R}).

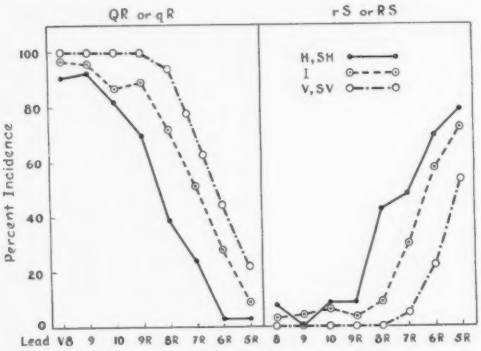

FIG. 5.—Per cent distribution of incidence of the QR or qR and of the rS or RS pattern in the back and right lateral leads, in three positional groups (vertical plus semivertical; intermediate; horizontal plus semihorizontal).

These leads were chosen because positional differences were more obvious than in the precordial leads. The reason might be the eccentric location of the heart, magnifying positional effects in V_8 to V_{5R} (fig. 1). The values (ordinate) are given in per cent of the incidence of the patterns. For this type of analysis, the groups V and SV, as well as H and SH, were combined in order to obtain numerically nearly identical positional groups (V + SV = 37 subjects; I = 33 subjects; H + SH = 33 subjects).

The regional trends are reversed for the QR (or qR) and the RS (or rS) pattern. The incidence of the QR (or qR) pattern is greatest in the group V + SV, and smallest in group H + SH. In contrast, the incidence of the RS (or rS) pattern is greatest in group H + SH and smallest in group V + SV.

Table 2 shows statistically significant differences between positional groups V and H in the regional pattern distribution, as calculated by means of the *t* test and the Cochrane-Cox test[15]. The *t* test can be used only when the variances in the two samples are of approximately the same magnitude. This was the case only for the midpoint of the QR, T− pattern. The Cochrane-Cox test was used for the other items, because it requires no assumption of similar variances. Table 2 shows both the *t* value and the corrected *t* values (columns 7 and 8). All differences are highly significant except that of the range of the qR, T− pattern, which is significant at the 0.05 level. In five items, there is only a 1:1000 probability that the results could be due to chance.

TABLE 2.—*Statistically Significant Differences in Regional Pattern Distribution*

Pattern	Group V		Group H		ΔM	*t*	*t* corr.	Signif.
	M	S. D.	M	S. D.				
Midpoint								
rS, T−	139.0	13.71	170.5	21.71	31.5	5.79	3.81	0.001
qR, T−	253.5	17.70	269.1	12.25	15.6	3.45	2.82	0.01
QR, T−	209.9	22.29	246.3	16.25	36.4	6.23	—	0.001
QS, T−	185.2	15.95	222.8	29.22	37.6	5.33	3.81	0.001
Range								
rS, T−	48.5	23.77	83.1	34.39	34.6	3.91	3.81	0.001
qR, T−	34.1	22.19	22.6	9.19	11.5	2.29	2.07	0.05
QR, T−	60.9	29.69	29.8	15.22	31.1	4.45	3.80	0.001

The graphs and tables presented so far give information about normal regional pattern distribution and their variability in different

positional groups. The relatively large variability within each positional group raises the question of the interindividual correlation between the location of various patterns. The qR, T+ pattern was arbitrarily chosen as a reference, and the correlation coefficients between its midpoint and the midpoints of the rS, T−; rS, T+; QR, T−; and qR, T_0 or T± patterns were calculated for the positional group I. They were, in above order, 0.59, 0.46, 0.31 and 0.82.

amplitude trends around the chest are also continuous. This is shown in figure 6. The abscissa is the location on the chest, both in terms of leads and degrees, and the ordinate refers to the mean amplitude (0.1 mv) or Q, R, S and T. The average magnitude and contour of the QRS-T deflections can be easily obtained from figure 6 for any location on the chest at the level of the heart, and for four electrical heart positions.

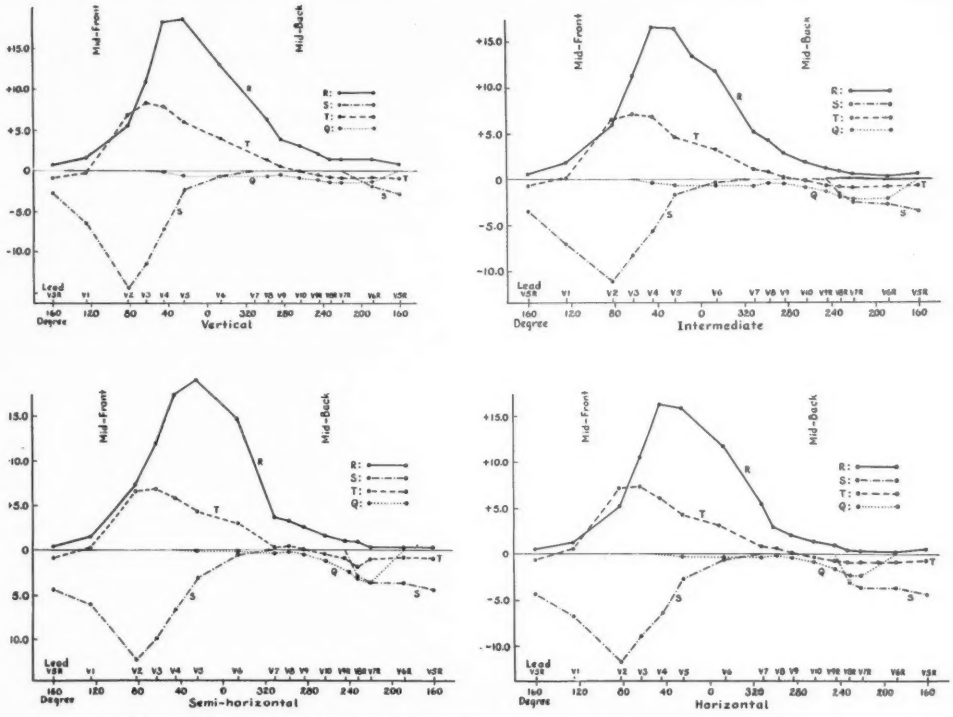

FIG. 6. Mean amplitudes of QRS and T deflections around the chest. Position is given in terms of V leads and degrees of angle.

All except the correlation to QR, T− were significantly different from zero, but they were also significantly different from 1 (perfect correlation). This means, that the position of one pattern determines also the position of the other patterns, but only to a certain degree. Other, nonspecified factors, interfere so that the correlation is not perfect.

Amplitudes

Since the transition of one pattern to the next is continuous, it can be implied that the

Since there are positional differences of the pattern distribution, positional effects on the amplitudes should also be expected. This is revealed by figure 6 and, more directly, by figure 7 and table 3. Table 3 shows a rather large number of items with positional amplitude differences reaching the level of statistical significance. The comparison was made between extremes of amplitudes in the direction from horizontal to vertical position. The results are quite consistent; the R wave in the precordial leads V_2 to V_6 is consistently smaller in the

more vertical position and consistently greater in the back and right lateral leads. The trends

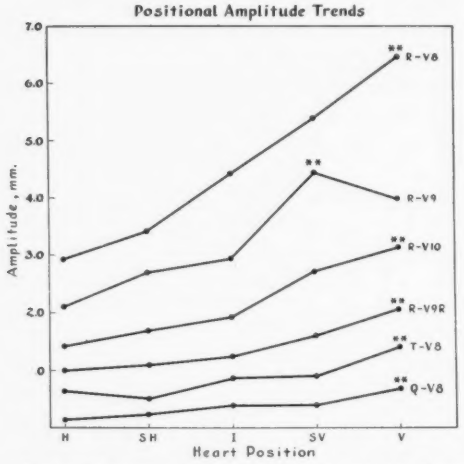

FIG. 7. Increase of amplitudes in back leads from horizontal to vertical position. ** = statistically high, significantly different from the mean amplitude in horizontal heart position.

TABLE 3.—*Significant Mean Amplitude Differences (Standardized mm.) between Different Heart Positions in Various Chest Leads. p = Level of Significance*

Lead	Defl.	Pos.	Mean	Pos.	Mean	Diff.	p
V_2	R	SH	7.38	SV	4.47	−2.91	0.05
V_3	R	SH	12.03	SV	6.69	−5.34	0.01
V_4	R	SH	17.42	SV	11.94	−5.48	0.05
V_5	R	SH	19.14	SV	13.73	−5.41	0.02
V_6	R	SH	14.79	SV	10.55	−4.24	0.01
V_8	R	H	2.93	V	6.46	+3.53	0.001
V_9	R	H	2.19	SV	4.47	+2.28	0.001
V_{10}	R	H	1.43	V	3.43	+2.00	0.001
V_{9R}	R	H	1.01	V	2.06	+1.05	0.001
V_1	R	H	1.24	I	1.81	+0.57	0.05
V_5	Q	H	0.24	V	0.57	+0.33	0.01
V_6	Q	H	0.30	V	0.67	+0.37	0.02
V_8	Q	SH	0.15	V	0.68	+0.53	0.001
V_{10}	Q	SH	1.12	SV	0.48	−0.64	0.05
V_{9R}	Q	SH	2.45	SV	0.64	−1.81	0.001
V_1	T	H	−0.24	V	0.55	+0.79	0.05
V_3	T	SH	6.85	SV	9.43	+2.58	0.05
V_4	T	SH	5.87	SV	8.02	+2.15	0.05
V_5	T	H	4.35	V	6.20	+1.85	0.01
V_6	T	H	3.15	V	4.14	+0.99	0.02
V_8	T	SH	0.48	V	1.43	+0.95	0.01
V_{10}	T	SH	−0.41	V	−0.03	+0.38	0.05

of the Q wave are reversed, with the dividing line approximately at V_9. The T− wave is consistently larger (or more positive) in leads V_1 to V_{10}. The absence of significant reversed T− wave trends in the opposite right lateral leads is probably due to its small magnitude. Figure 7 shows the positional trends in some of the items of table 3.

There is a considerable interindividual variability of the amplitudes of all deflections, comparable to the interindividual variability of pattern distribution, with S.D.'s amounting to one-third or more of the means.*

DISCUSSION

It is not surprising that the rotation of the heart around a sagittal axis, as defined by the five "electrical" heart positions, has a definite effect on the pattern distribution and magnitude of amplitudes in the horizontal plane (rotation around the long axis of the heart). The arbitrary definition of the three axes of rotation (sagittal, transversal, long axis) has been recognized for some time.[16, 17] The actual displacement of the heart, with reference to a "normal" position, is always three-dimensional, involving all axes. However, until now there has been available no quantitative material, in the sense of our analysis, which could be used as a background for routine electrocardiographic interpretation.

The potential value of the present material for clinical electrocardiography may be illustrated by discussion of the distribution of the qR, T− pattern. Appearance of this pattern in V_1 is usually diagnosed as right ventricular preponderance. In the absence of such a pattern in V_1 in suspected right ventricular preponderance, it has been suggested to take leads farther to the right.[6–8] Our material shows that the qR, T− pattern extends much farther to the right in the vertical position than in the horizontal position. A qR, T− in V_{6R} would still be within the 95 per cent normal limits in a person with a vertical heart, while it would be outside the normal limits, and probably indicative of right ventricular preponderance in a patient with horizontal, semihorizontal or intermediate heart position. It should be kept in mind that the 95 per cent range limits are conservative, that is, in 5 per cent of normal

* Tables with the means and standard deviations of the amplitudes are deposited in the American Institute of Documentation.

population a qR, T− might be found even farther anterior-lateral, for instance in V_{5R}. Since right ventricular preponderance is usually associated with vertical or semivertical heart position, the validity of the diagnosis of right ventricular hypertrophy from the presence of a qR, T− pattern in leads to the right from V_1 is questionable.

The same pattern (qR, T−) which would be diagnosed as right ventricular preponderance in right lateral leads, might be diagnosed as coronary insufficiency when found in the left lateral or left back leads. This pattern extends to approximately V_8 in vertical heart position and to V_7 in the other heart positions.

Using the criteria of other leads (V_6, V_L or V_F), in the absence of direct information, for the interpretation of back leads[10] may lead to a false diagnosis of coronary insufficiency in an appreciable proportion of normal subjects. The incidence of the qR, T− or the QR, T− pattern in the left back leads might be considerably higher in a population of patients with coronary insufficiency, but the overlapping of normal population and a population of patients interferes with the use of this pattern in that particular location for diagnostic differentiation.

We have used the five "electrical" heart positions for the subdivision of positional groups, following accepted electrocardiographic routine. Several authors found a high correlation between anatomic and electrical heart position in the frontal plane,[17–19] but marked ventricular enlargement might interfere with the correlation.[9] Actually, the demonstration of significant differences of pattern distribution and amplitudes in the five positional groups shows the validity of this procedure for electrocardiographic differentiation.

The correlation between anatomic and electrical heart position was much less pronounced in the horizontal plane.[19] This might explain, in part, the fact that the interindividual correlation between the location of the qR, T+ pattern (as reference) and the location of other patterns is not perfect.

The results have some bearing on the fundamental theory of electrocardiographic interpretation. The extremes of pattern distribution cannot be easily reconciled with the projection of specific local patterns to the nearest electrode position.

Duchosal and Sulzer,[20] starting from vectorcardiography, arrived at the conclusion that the patterns found on the surface of the chest are projections of an integrated central vector, and this view was supported by Meyer and Herr,[21] by Grant,[22] and by Scherlis and Grishman.[23] This hypothesis implies that mirror patterns will be found at opposite ends, with reference to a center in the heart.

In our material, the average difference of the midpoints of the mirror patterns qR, T+ and rS, T− pattern was 190.2 degrees and was statistically not significantly different from a straight line (180 degrees). This agrees with the expectation of mirror patterns at opposite ends, and also shows that the arbitrary determination of our center must have approached its average location.

It should be noted, however, that the interpretation of mirror patterns, by way of inspection, ignores possible phase differences. A more direct approach was developed,[24, 25] and will be discussed in forthcoming communications.

It should be emphasized, however, that the main purpose of this study was to present actual material on a sound basis of statistical evaluation, regardless of electrocardiographic theory.

Summary

1. In 103 healthy middle-aged men, subdivided in five groups according to the electrical heart position (vertical, semivertical, intermediate, semihorizontal, horizontal), 15 symmetrically spaced leads were taken around the chest.

2. The location of the leads was defined in terms of degrees with reference to a hypothetic center in the heart which was obtained by means of measurements on frontal chest films.

3. The means, standard deviations and upper and lower limits for 95 per cent of the normal population were calculated for the midpoints and endpoints of the following patterns: rS, T−; rS, T+; RS, T+; qR, T+; qR, To; qR, T−; QR, T+; QS, T+.

4. There is a continuous transition from one

pattern to the next, together with a considerable interindividual overlapping of pattern distribution.

5. The range (defined as the difference of the endpoints) of most patterns shows also large variability. It may be so wide that it is difficult to relate it consistently to specific parts of the heart, and it may be so narrow that it could be missed at the usual distance between electrode positions.

6. Significant differences in the pattern distribution were found in the different positional groups.

7. There was a significant correlation between the location of the qR, T+ pattern as reference and four other patterns, but the correlation was not perfect.

8. The means of the amplitudes of Q, R, S and T versus location (degrees or lead) are presented in graphs which permit intrapolation and reconstruction of the average electrocardiogram for any location on the chest circumference, and for any heart position.

9. There were significant amplitude differences in the various positional groups.

10. The interindividual variability of the amplitudes is also quite large, comparable to that of pattern distribution.

11. The material presented can be used as normal standards for back and lateral leads. The significance for diagnosis of right ventricular preponderance and coronary insufficiency of the posterior-lateral wall is discussed.

12. The bearing of the results on some theoretic aspects of electrocardiographic interpretation is discussed.

Acknowledgment

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Clinical Studies on Veratrum Alkaloids

II. The Dose-Response Relations of Protoveratrine in Hypertension

By Edward Meilman, M.D., and Otto Krayer, M.D.

An extensive study of the hypotensive properties of protoveratrine, a pure crystalline ester alkaloid from *Veratrum album*, has been made in hypertensive and normotensive individuals. This drug is shown to be capable of lowering the blood pressure in hypertension of varied etiologies including essential hypertension, acute or chronic renal disease, malignant hypertension, toxemia of pregnancy, and carcinoma of the adrenal cortex. The relationships between dose and response from single intravenous, continuous intravenous, intramuscular and oral administration have been determined.

IT WAS SHOWN in a previous communication[1] that protoveratrine has a hypotensive and cardiodecelerator effect in human hypertension. Although the alkaloid possesses a narrow therapeutic range it may find some application in the therapy of hypertensive disorders. The practical usefulness of a drug, as a tool in the study of human physiology, or as a therapeutic agent, depends upon accurate knowledge of the relation between dose and response. As a rule, this relation varies with the route of administration. Hence, the studies reported earlier were extended to yield information on the influence of the route of administration upon the effect of protoveratrine on blood pressure and heart rate.

Method

Ten normal persons as well as 83 patients with hypertension of various origins were used for this study. The administration of protoveratrine was by single intravenous injections (284 injections in 71 patients and three normal subjects); by continuous intravenous infusion (46 infusion experiments in 20 hypertensive patients and seven normal individuals); by intramuscular injections (over 350 injections in 32 patients) and by the oral route (2 to over 800 doses in 15 patients). Most of the patients were ambulatory, coming into the hospital only for the duration of the study.

The protoveratrine used in these studies was pure crystalline material.* The infrared absorption spectrum of both samples was identical with that of the protoveratrine prepared by W. A. Jacobs which was used in the earlier studies. Melting point and rotation of the three samples did not differ significantly. Likewise the hypotensive responses obtained with the three samples of protoveratrine were indistinguishable.

For the intravenous administration single injections of a solution of 1:10,000 were used, while continuous infusions were made with dilute solutions of protoveratrine (0.5 to 1.5 μg. per cc. of 0.9 per cent sodium chloride solution or .5 per cent glucose solution) at desired rates. Most of the infusions were carried out for four to six hours; two lasted eight hours and one 96 hours. In 17 experiments the blood pressure was lowered by a single suitable intravenous injection. In 29 experiments the blood pressure fall was induced in a more gradual fashion (20 minutes to two hours) by administration of protoveratrine at rates of 1.8 to 7 μg. per minute, following which the blood pressure was maintained at a steady low level by the continuous infusion of very small amounts of protoveratrine (0.6 to 2.0 μg. per minute).

For the intramuscular injections solutions of 1:2000 were used. In order to prevent pain at the site of intramuscular injection, 1.0 to 2.0 per cent procaine hydrochloride was usually added. A 1 cc. graduated syringe and a number 25, ¾ inch needle were used for these injections.

Solutions of 1:1000, compressed tablets, or time-disintegrating tablets† were used for oral medication. The dose per tablet was 0.1 mg. or 0.5 mg.; the

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* Generously supplied by Eli Lilly and Company, Indianapolis, Ind., and by Lederle Laboratories, Pearl River, N. Y.

† Supplied by Eli Lilly and Company.

TABLE 1.—*Responses of a Typical Group of Patients with Hypertension of Different Etiologies to the Intravenous Administration of Protoveratrine*

Patient Sex Age	Diagnosis	Known Duration of Hypertension	Dose			B.P.‡		H.R.‡	
			mg. i.v.	μg/Kg.	μg/sq. m.	Before	After	Before	After
1. B.Cr. F 50	Ess. hypert. Cong. heart failure	7 yrs.	0.10 0.11 0.12	1.64 1.74 1.9	61.3 67.5 73.6	176/92 180/96 200/96	148/74 124/70 126/60	70 64 64	52 48 36
2. S.E. F 50	Ess. hypert.	8 yrs.	0.107	1.88	68.6	198/120	118/82	58	50
3. J. F. F 48	Ess. hypert.	5 yrs.	0.108 0.12	1.67 1.86	66.6 74.0	184/120 190/116	128/90 104/74	76 70	60 54
4. S.M. F 50	Ess. hypert. Ang. pect.	10 yrs.	0.10 0.12 0.14	1.41 1.69 1.97	56.8 68.1 79.5	200/130 210/128 210/128	164/110 132/88 106/74	84 60 72	72 56 56
5. B.M. M 43	Ess. hypert.	6 yrs.	0.10 0.12 0.14	1.56 1.87 2.19	59.2 71.0 83.0	186/124 180/112 190/120	160/110 130/86 110/78	92 84 76	80 76 56
6. I.R. F 45	Ess. hypert.	15 yrs.	0.10 0.14	1.73 2.43	63.2 88.5	176/118 178/120	152/104 130/90	92 84	80 72
7. R.L. F 51	Ess. hypert.	4 yrs.	0.10	1.72	68.0	176/110	124/86	78	72
8. J.S. M 62	Ess. hypert.	10 yrs.	0.14	1.84	72.1	244/140	128/84	72	52
9. A.N. F 52	Ess. hypert.	12 yrs.	0.14 0.19	2.0 2.76	82.3 112.0	230/116 220/116	220/110 152/90	64 60	56 52
10. M.R. F 56	Ess. hypert.	10 yrs.	0.13 0.17 0.20	1.87 2.45 2.90	77.4 101. 119.	194/110 190/116 190/116	180/104 160/100 150/92	96 84 100	80 76 78
11. R.S. F 60	Ess. hypert.	4 yrs.	0.09	1.5	57.6	200/110	152/92	80	76
12. C.McC. F 36	Ess. hypert.	5 yrs.	0.10	1.76	63.6	196/124	118/82	108	80
13. J.P. M 62	Ess. hypert.	4 yrs.	0.10 0.12	1.38 1.66	55.9 67.0	174/114 198/116	126/84 114/74	70 88	64 74
14. O.M. F 36	Ess. hypert.	4 yrs.	0.10	1.89	64.2	160/110	114/76	104	70
15. J.G. F 52	Ess. hypert.	7 yrs.	0.12	1.66	71.4	224/136	130/86	74	60
16. E.P. F 45	Chr. gn.	8 yrs.	0.11 0.13	2.30 2.72	75.8 89.6	186/112 174/108	142/90 124/76	64 62	56 56
17. J.H. M 29	Chr. gn.	6 yrs.	0.12	1.83	66.0	198/128	130/86	84	64

TABLE 1—*Continued*

Patient Sex Age	Diagnosis	Known Duration of Hypertension	Dose			B.P.‡		H.R.‡	
			mg. i.v.	μg/Kg.	μg/sq. m	Before	After	Before	After
18. H.F. F 39	Chr. gn.	8 yrs.	0.10	1.33	54.6	208/130	160/110	80	72
19. B.C. F 64	Nephrotic Syndrome	10 yrs.	0.10	1.10	52.0	180/100	152/86	76	68
20. F.G. F 39	Malig. hypert.	3 mos.	0.10	1.77	61.8	180/114	140/92	100	92
21. T.B. F 26	Eclampsia	1 day	0.14	2.20	81.0	146/110	124/96	112	88
22. Y.M. F 50	Carc. adr. cortex	1 yr.	0.11	1.61	65.0	164/110	116/78	92	68
23. C.Bl.* M 10	Chr. gn.	5 yrs.	0.07	2.41	—	162/124	130/80	92	76
24. C.B.* F 10	Acute gn.	(?)1 week	0.08	2.29	—	164/118	144/94	76	54
25. E.H.* M 9	Acute gn.	(?)1 week	0.055	1.66	—	152/112	136/100	96	70
26. L.P.† M 43	CNS lues, asympt.	—	0.107	1.6	59.0	102/70	100/64	68	64

* Patients 23, 24 and 25 are children. We are indebted to Dr. Margaret Maroney, Children's Medical Center, Boston, for the data in these three cases.

† Patient 26, L.P., a normotensive, is listed for comparison.

‡ B.P. and H.R. before are the lowest levels of blood pressure and heart rate recorded during the control period preceding injection. B.P. and H.R. after are the lowest blood pressure and heart rate recorded for at least two readings following the injection.

tablets were scored so as to facilitate adjustment of dosage.

Blood pressure measurements were made with a mercury sphygmomanometer in the usual manner and unless otherwise indicated denote the pressure in recumbency, except that blood pressure measurements in the studies with oral medication were in the sitting position. In most instances readings were made by the same two observers. Patients whose blood pressure could be influenced by placebo or who obtained marked reduction on bed rest were excluded from this study. Some of the patients who received oral protoveratrine had blood pressure readings taken at home, either by the patient or by a carefully instructed member of the family, as described by Ayman and Goldshine.[2] Control studies have included administration of placebo and inadequate doses of protoveratrine.

INTRAVENOUS ADMINISTRATION

As was pointed out earlier,[1] when protoveratrine is given intravenously to an individual patient the response is not only repeatable but predictable. Moreover, in a given patient within a certain dosage range, increasing the dose increased the fall in both systolic and diastolic pressure (B.Cr., J.F., S.M., B.M., M.R. in table 1). The relation between the increase in dose and increase in duration of action is less clear, although in general, larger doses caused greater duration of action. The response in the individual patient is so constant that a patient with known reaction to the drug can be used to assess the strength of an unknown protoveratrine solution. However, the variation from patient to patient in the response to a given dose is quite marked. It can be seen from table 1, which gives data on the response to intravenous protoveratrine of a group of patients with hypertension of different etiologies, that a

very good hypotensive response (that is, a fall of blood pressure to or near the normal range) follows doses of the order of 1.6 to 1.9 μg. per kilogram of body weight in most of the patients listed. Figure 1, which gives data on 51 patients (including the adult hypertensives in table 1), illustrates that a fall of blood pressure to or below 150 mm. Hg systolic and/or below 90 diastolic occurred in two-thirds of the patients with intravenous doses of 1.5 to 1.9 μg. per kilogram. However, some patients required considerably larger amounts. Only a few patients responded to doses less than 1.5 μg. per kilogram. This variation in dosage is

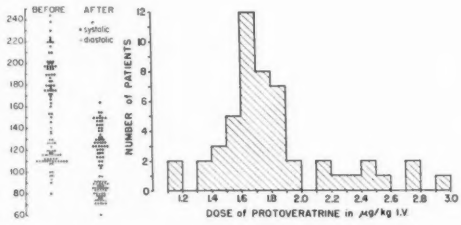

FIG. 1. The range of dosage of protoveratrine in micrograms per kilogram, intravenously, to lower the blood pressure to or below 150 mm. Hg systolic and/or 90 diastolic in 51 adult hypertensive individuals regardless of the initial blood pressure level. The actual systolic and diastolic readings before and after administration of protoveratrine to these 51 patients are charted on the left.

apparently not related to the duration of the hypertension or its etiology (table 1).

In the previous report[1] the dosage range studied was 0.08 to 0.20 mg. The highest dose given since then is 0.22 mg. Two patients have received 0.20 mg. in a single intravenous injection with a good vasodepressor response and no disturbance of cardiac rhythm or nausea. However, doses of this magnitude would cause nausea, vomiting, profound hypotension or disturbances in cardiac rhythm in most patients.

In view of the variation in dosage the evaluation of the vasodepressor properties of protoveratrine in a given patient requires the exploration of a range of increasing doses. The determination of a suitable intravenous dose should follow one of these plans: (A) An initial dose of 0.10 mg. of protoveratrine is given intravenously, slowly over two minutes. In a patient who is small, or well-digitalized, even less, 0.08 to 0.09 mg., might be used for the first trial. If no hypotensive response follows, the next dose given three to four hours later may be increased by 0.02 mg. until suitable effects are obtained. Once a dose of moderate hypotensive action is found, increments of only 0.01 mg. will cause measurably greater vasodepressor action. (B) If it is desired to obtain a prompt response, the initial dose of 0.10 mg. may be followed by 0.02 mg. at 10-minute in-

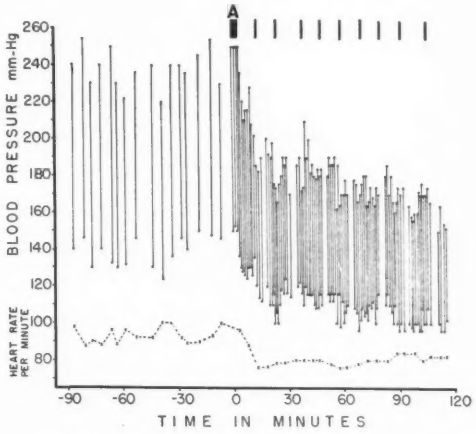

FIG. 2. I.K., a 57 year old man, with severe hypertension of 20 years' duration. The response of blood pressure and heart rate to protoveratrine administered by repeated intravenous injections is shown. At *A*, 100 μg. was given. Subsequent injections, indicated by the short vertical bars, were each 20 μg. at approximately 10-minute intervals. There was no nausea. The observations were made during measurement of renal clearances.

tervals until a suitable low level is reached (fig. 2). Injections must be at least 10 minutes apart since this is the time required to obtain the maximum effect from the preceding dose and measurements of blood pressure and heart rate should be made every two minutes during this period.

Duration of action of a single effective intravenous injection is one to three hours,[1] occasionally longer. Durations greater than three hours are difficult to evaluate since in some instances control blood pressure levels may not be regained for as long as 12 hours. However, repetition of the same dose within two hours

will cause a significantly greater hypotensive response.

Toxicity. The range between an effective and a toxic dose is relatively narrow. A patient who responds to 0.1 mg. with a good hypotensive reaction free of side effects, may have nausea, epigastric and substernal discomfort, marked hypotension, bradycardia or even arrhythmias after 0.13 mg. The administration of atropine, 0.5 to 0.8 mg. intravenously or 1 mg. subcutaneously, will prevent or abolish the bradycardia or arrhythmia, but is without effect on the nausea or substernal discomfort. With proper attention to dosage, vomiting need not occur after single intravenous administration. We have had no instances of vomiting in a series of 284 injections. Nausea or substernal discomfort appeared 18 times.

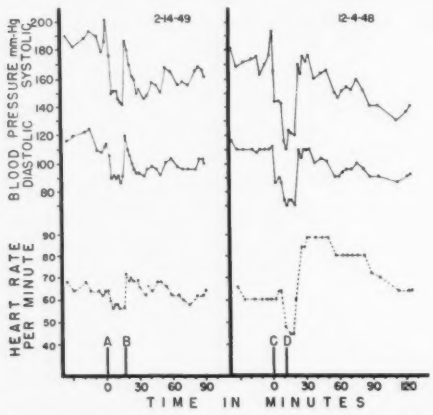

FIG. 3. E.P., a 45 year old woman with chronic glomerulonephritis and hypertension. At *A*, 0.11 mg. of protoveratrine was injected intravenously; at *B*, 0.4 mg. atropine sulfate intravenously. There was a prompt rise in blood pressure to control values coincident with the acceleration of heart rate, but the blood pressure soon fell although the bradycardia was not restored. The same phenomenon is illustrated in an exaggerated form on the right. At *C*, 0.16 mg. protoveratrine was given intravenously and at *D*, 0.8 mg. atropine sulfate subcutaneously. It is quite obvious that the hypotensive effect returned despite an increase in heart rate.

Marked bradycardia, as well as nausea, is more likely in patients who are digitalized. A woman aged 64, weighing 51 Kg., who had been taking 0.2 mg. digitoxin daily, developed bradycardia with numerous extrasystoles after only 0.08 mg. of protoveratrine intravenously. Injection of 0.8 mg. atropine sulfate intravenously stopped the bradycardia and extrasystoles. However, despite a spontaneous bradycardia or digitalization one may occasionally obtain a good hypotensive response from protoveratrine without further slowing of the heart rate.

In seven patients, of the 71 studied, a limiting factor in obtaining a good hypotensive response was the appearance of marked slowing of the heart, out of proportion to the fall in blood pressure, with nodal rhythm (one patient) or ventricular extrasystoles (one patient). Three of the seven patients were on maintenance doses of digitoxin.

Severe hypotensive effect is best counteracted by ephedrine sulfate, 25 mg. or more subcutaneously. Epinephrine is also effective. The patient should be kept flat and not allowed to walk about during a severe hypotensive reaction (for example, under 90 mm. Hg systolic). It is not unusual to see a blood pressure fall to as low as 90/50 without any subjective discomfort to the patient other than a sense of lightheadedness.

Atropine usually exerts only slight moderating effects on the hypotensive response,[1] but occasionally it may cause a temporary rise in blood pressure to control levels or higher (fig. 3). However, after the tachycardia has subsided and the heart rate regained control values, the blood pressure falls distinctly below its control level. This emphasizes again that the hypotensive effect of protoveratrine is not dependent on the presence of bradycardia, although greater vasodepressor action is observed at slow heart rates. This type of response to atropine (fig. 3) is similar to that reported by Assali and co-workers when tetraethylammonium chloride is given during the maximum action of Veratrone.[3] They suggested that it indicated a blocking effect of tetraethylammonium chloride on the neurogenic mechanism responsible for the hypotension. The occurrence of a similar response after atropine, however, suggests that this transient rise in blood pressure may not necessarily be due to the ganglionic blocking action. It may be the result of the

tachycardia (and rise in cardiac output) which follows both tetraethylammonium chloride and atropine.

Continuous Intravenous Infusion

Since protoveratrine is eliminated slowly and since its effects are probably a function of the concentration of the drug at the sites of action, continuous intravenous infusions were given to see (1) at what rate elimination proceeds in the human organism, (2) whether maintaining the concentration of the drug at a constant level would result in steady levels of blood pressure and (3) whether graded hypotensive responses could be obtained by varying the rate of infusion.

Three typical experiments on one patient, a woman with malignant hypertension, are shown in figure 4. A control experiment with 1 μg. per minute for over four hours was without effect; 2 μg. per minute lowered the blood pressure to normal in two hours and 3 μg. per minute in one hour. Thereafter, 1.1 μg. per minute sufficed to maintain the blood pressure at an essentially steady level as long as the infusion was continued.

Since the rate of infusion of drug capable of maintaining a steady blood pressure level must equal the amount which is eliminated by the body, it was possible to determine this value from such experiments. The values found ranged from 0.6 to 2.0 μg. per minute. For 15 of 20 hypertensive patients it appeared to be of the order of 1 μg. per minute.

If the size of the initial hypotensive dose is known (see fig. 1), as well as the rate of infusion necessary to maintain a steady low blood pressure level, it is possible to calculate the approximate time necessary to lower the blood pressure to normal with any desired rate of infusion of protoveratrine. As the rate of administration of the protoveratrine solution is increased, the time required to induce a good hypotensive effect decreases. At 2 μg. per minute the time required to lower the blood pressure to "normal" (120–130/80–90 mm. Hg) varied from 70 to 114 minutes (four patients); at 3 μg. per minute, the time was 37 to 70 minutes (five patients); at 4 μg. per minute, 24 to 43 minutes (six patients).

When the rate of administration is very rapid, the response becomes similar to that of a single intravenous injection. For example, one patient (E.P., table 1) received 60 μg. per minute for two minutes, followed by 0.75 μg. per minute for four hours. There was a rapid hypotensive effect reaching a maximum in seven minutes, after which the blood pressure was maintained at an essentially constant and normal level throughout the duration of the infusion. When the infusion was discontinued

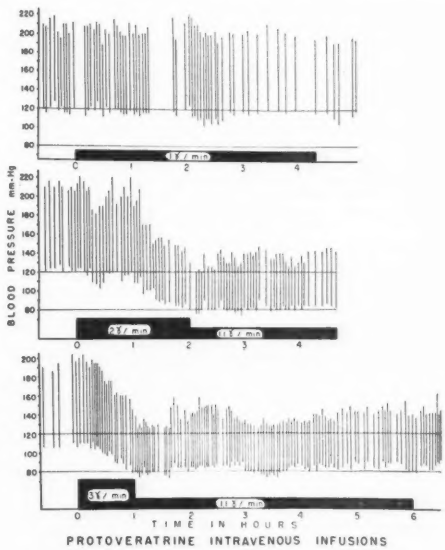

Fig. 4. A.M., a 37 year old woman with malignant hypertension. The black bars indicate continuous intravenous infusion of protoveratrine in micrograms (γ) per minute. For further explanation see text.

the blood pressure rose slowly during the next four to five hours to control levels. During the continuous infusion side effects were absent. In fact, the patient's symptoms of hypertensive encephalopathy (headache and nausea) were strikingly alleviated. Although nausea may appear as a result of excessive amounts of the drug, in this instance nausea, present continuously for a week, disappeared with the fall in blood pressure and the patient was able to eat during the infusion with no discomfort. At the same time her headache became much less severe. When the blood pressure rose again

her headache returned in its original intensity; the nausea recurred but in lessened degree.

Close attention is necessary during infusion at rapid rates since it would require only a short time to introduce a dose considerably in excess of that required for optimal hypotension free of side effects. Since the maximum effect of the drug does not appear for about 10 minutes, an excessive dose might easily be given during this time, resulting in nausea, vomiting and probably profound hypotension. For example, at 5 μg. per minute, 10 additional minutes of infusion would probably raise the total administered dose to toxic levels. As a rule the infusion should be reduced to 1 μg. per minute after administration of a dose equal to the priming dose (see fig. 1), plus 1 μg. for every minute of the infusion. At slower rates of infusion, such as 2 to 4 μg. per minute, a satisfactory response will be obtained if the rate of the infusion is decreased to 1 μg. per minute when the systolic level has fallen to 140 to 150 mm. Hg. A steady state at about 120 to 130 mm. Hg systolic will be reached during the following 10 to 15 minutes.

Administration of protoveratrine to normotensive individuals at rates which would cause significant blood pressure lowering in hypertensives may cause no change in blood pressure or a modest fall. A normal woman who received 100 μg. intravenously, followed, after a five-minute delay because of slight nausea, by 1 μg. per minute for over three hours, showed no change in blood pressure. A normal male who received an infusion at 3.8 μg. per minute for 45 minutes had a fall in blood pressure from 126/85 to about 110/70, this level being maintained by 1 μg. per minute for three hours thereafter. This slight fall should be contrasted with the characteristic marked decrease in blood pressure in a hypertensive patient shown in the lower portion of figure 4.

Bradycradia, which may be excessive after single intravenous injections (100 to 130 μg.) of protoveratrine, is usually not severe during infusions of relatively dilute protoveratrine solutions (1 to 4 μg. per minute) although slowing of the heart does occur.

The intravenous administration of protoveratrine by continuous infusion thus makes it possible to lower the blood pressure to desired levels in a controlled fashion. Although such technics may have limited clinical application, they are of importance in physiologic studies in which the maintenance of a steady lowered blood pressure level is necessary to compare data in the hypertensive state with data at normotensive levels.

Intramuscular Administration

Prolonged vasodepressor action as well as greater ease of administration is afforded by intramuscular injections of protoveratrine. As would be expected, the vasodepressor action after intramuscular injection is not as quantitatively reproducible in the same patient as after intravenous administration, probably due to variations in absorption. The effective intramuscular dose was found to be two and one-half to three and one-half times the effective single intravenous dose. To establish the intramuscular dose in a previously untested patient we begin with an initial dose of 0.30 mg. If this is completely ineffective, subsequent doses, at intervals of eight hours, are increased by 0.05 mg. If a dose is reached which causes a moderate hypotensive effect, the next dose is increased by only 0.03 mg. The largest single intramuscular dose we have used was 0.6 mg. in a patient who tolerated 0.2 mg. intravenously (A.N., table 1). The dose of 0.6 mg. is unusually large and it caused nausea in this case, but even smaller doses (0.45 to 0.50 gm.) may cause vomiting in susceptible individuals. In adults, on the basis of body weight, the average intramuscular dose in over 32 adult patients was 4 to 6 μg. per kilogram. Studies on a small group of four children indicate that 3 to 5 μg. per kilogram appears to be a suitable intramuscular dose.

Noticeable blood pressure decreases after intramuscular injections do not appear earlier than 20 minutes following injection. A maximum effect is reached in 30 to 60 minutes. A good hypotensive response usually persists for four to six hours, occasionally as long as 12 hours. It is not possible to increase the duration of action further by increasing the size of the dose. Cumulative action usually occurs if the drug is administered in the same dose at in-

tervals of less than eight hours. Repeated administration at 8 to 12 hour intervals can be carried out. Figure 5 illustrates the blood pressure variations during five days of intramuscular administration to a patient with essential hypertension. On the last day, a slight increase in dosage caused a marked hypotension. Nausea and vomiting did not occur. However, when her blood pressure fell to 80/40 she felt very faint in the erect position and had to remain recumbent until her pressure rose to 100 to 110 mm. Hg systolic.

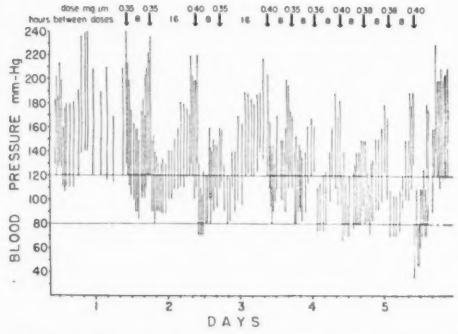

FIG. 5. J.F., a 52 year old woman with essential hypertension. Repeated intramuscular injections of 0.35 to 0.40 mg. of protoveratrine were given at 8 or 16 hour intervals. The restoration of control blood pressure levels occurs in this case in about eight hours.

The drug has been given intramuscularly repeatedly, usually at intervals of eight hours, for periods of a few days to six weeks. One patient received 90 consecutive intramuscular injections at 8 or 12 hour intervals over 42 days without change in the effectiveness of the drug. Two patients have shown less effect to the same dose of the drug, one after seven and one after 10 days, but a good hypotensive effect could be secured by a larger dose, although the incidence of nausea and vomiting became greater. Both of these patients were receiving digitalis, and the change in their responsiveness might have been related to the action of digitalis.

The warmth, which is such a characteristic part of the immediate subjective response to intravenous injection, is of only minor degree after intramuscular medication. Nausea and vomiting, when they occur after excessive doses, are apt to be quite severe and may last for 30 minutes.

ORAL ADMINISTRATION

Protoveratrine exerts its hypotensive as well as its toxic effects when given orally.

Studies have been made in a small group of 15 patients all of whom responded suitably to intravenous administration of protoveratrine. Eleven of them had essential hypertension (one in a malignant phase) and four had chronic nephritis and hypertension (two in the malignant phase). In this group, initial studies were made in the hospital with observations of blood pressure and pulse rate every half to one hour during the day. Three patients now take the drug on an outpatient status with blood pressure readings at home,[2] usually four times daily, with four readings at five-minute intervals each time. Blood pressure measurements are made by the patient or a member of the family.

In 5 of 15 patients (including one with malignant hypertension) no significant reduction of blood pressure could be obtained, even with doses that caused nausea, weakness or extreme bradycardia. In six of the patients moderate but inconstant and probably insignificant reductions of blood pressure were obtained. In four of the patients, significant* reduction of blood pressure during part of the day could be obtained for long periods (three to seven months) with occasional episodes of nausea and vomiting. One patient of this group of four suffered a severe hypotensive reaction with fall in blood pressure from 220/120 to 80/40, but recovered uneventfully without treatment.

The daily dose ranged from 1.0 to 2.5 mg. in three to five divided doses, preferably taken after meals and at bedtime, at intervals of four to six hours.

On the basis of this small group of patients, it has not been possible to establish any relation between the intravenous and the oral dose. The proper dosage is arrived at by trial, starting with 0.5 mg. at 9 a.m., and 0.25 mg. at

* The differences between the average systolic and diastolic blood pressures during drug and control (placebo) periods are greater than twice the standard error of the difference between the two means.

3 p.m. and 9 p.m. The size of the last two doses is raised in turn to 0.5 mg. and then the interval between doses is shortened and a fourth or even fifth dose added until an effect appears.

A portion of the record of home blood pressure readings of one of the favorable group of four patients is shown in figure 6. This patient is a 62 year old active stockbroker. Each dot represents the average of four readings taken by his son. The abrupt rise on substitution of placebo and fall on resumption of protoveratrine is notable and has been repeated several times. In this patient, initial control readings were 190–220 systolic and 110–130 diastolic. During administration of protoveratrine most of the systolic readings fell below 190 and most of the diastolic readings below 110. During placebo periods the readings were usually above 190 systolic and 110 diastolic.

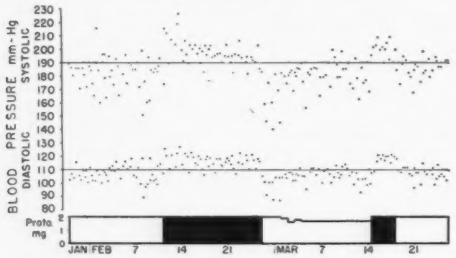

FIG. 6. J.S., a 62 year old man with essential hypertension. Each dot represents the average of four readings, systolic and diastolic, taken by his son. Measurements were made three or four times daily. Neither the patient nor his son knew when placebo medication was substituted for protoveratrine. The solid black areas represent the time during which placebo was given. This chart represents the last two and one-half months of a study lasting over six months, which contained a similar placebo period earlier.

In figure 7 is shown the actual blood pressure readings on three typical days during a seven-month period of study of another patient, a 42 year old housewife who had a bilateral thoracolumbar sympathectomy one and one-half years before for malignant hypertension. Her papilledema cleared but her blood pressure measurements remained unchanged. She received protoveratrine orally for seven months without evidence of tolerance. She was able to carry on all household duties including care of a young child during this time. The first day shown in figure 7 is the last day of a placebo period, the next two are on resumption of protoveratrine. When the drug is administered orally, one may see considerable variation in blood pressure readings during a single day and from one day to the next. It is quite obvious from figure 7 that the result depends on what time of day the blood pressure determination was made. Moreover, a larger oral dose (as on the third day) does not necessarily give a greater hypotensive response. It is also apparent that blood pressure control is achieved during only part of the day.

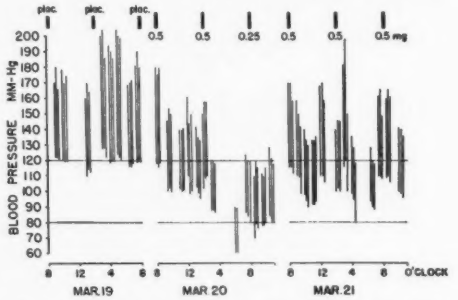

FIG. 7. M.B., a 42 year old woman. This represents three typical days out of a seven-month period on oral protoveratrine. Blood pressure measurements were taken by the patient. March 19 is the last day of a two-week placebo period and March 20 and 21, the first two on resumption of protoveratrine. The patient voluntarily took one-half the dose at 8 p.m. on March 20 because she noted how low her blood pressure was.

A patient who can cope with an occasional spell of nausea or vomiting or a rare severe hypotensive reaction may take the drug for long periods (six to seven months). Evaluation of benefit to be derived from such a program will require prolonged study. However, there is striking alleviation of subjective symptoms, such as headache, with reappearance of these symptoms on substitution of placebo therapy.

SUMMARY

The dose-response relations of protoveratrine in man have been studied in 83 hypertensive and 10 normal persons, with 284 intravenous injections, 46 continuous intravenous infusions, over 350 intramuscular injections and over 2000 oral doses.

A good hypotensive effect lasting one to three hours was usually obtained with intravenous doses of 1.5 to 1.9 μg. per kilogram. In a given individual a suitable hypotensive effect could be obtained either by exploring a range of slowly increasing doses or by giving an initial dose of 0.1 mg., followed by 0.02 mg. at 10-minute intervals. A marked bradycardia, especially in digitalized patients, may prevent attainment of a satisfactory low blood pressure. Atropine and ephedrine, respectively, are effective agents against excessive bradycardia and hypotension due to overdosage.

Administration of protoveratrine by continuous intravenous infusion at rates of 2 to 7 μg. per minute make it possible to obtain graded hypotensive responses. The lowered level can be maintained at a steady state for many hours by infusions of the order of 1 μg. per minute.

Intramuscular injections, in doses of 4 to 6 μg. per kilogram, have been given at intervals of 8 to 12 hours for as long as six weeks with good hypotensive effects.

Oral administration produced significant blood pressure lowering in only 4 of 15 patients who took the drug for three to seven months, without evidence of tolerance. There were occasional episodes of nausea and vomiting and there was one severe hypotensive reaction.

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The Lewis A. Conner Memorial Lecture

The Heart and the Thyroid: with Particular Reference to I^{131} Treatment of Heart Disease

By HERRMAN L. BLUMGART, M.D., AND A. STONE FREEDBERG, M.D.

The physiologic, pathologic, and clinical interrelationships between the thyroid and the cardiovascular system are discussed. The therapeutic effects of hypothyroidism induced by I^{131} to lessen the work of the heart are described in 39 euthyroid patients with intractable advanced angina pectoris or congestive failure. Only patients were treated who were seriously incapacitated despite all conventional forms of therapy for many months or years. The results of two confirmatory series of cases similarly treated by others are reviewed.

WE ARE assembled here at this time to express our respect and esteem for Dr. Lewis Atterbury Conner through this lectureship established in his honor. In reality, *all* the activities of the American Heart Association are a lasting tribute to him. For he was one of its founders, the creator and first editor of the *American Heart Journal*. Particularly at this moment, six months after his death on December 4, 1950, it is gratifying to know, that regardless of the time and the place of our meetings, and regardless of the changing program committees, Dr. Lewis A. Conner will always, through this lectureship, participate in the scientific proceedings of our association.

But long before his 83 years had ended, he had become an unforgettable legend. For his was a vibrant and compelling personality. Poise, reserve, dignity, and an almost austere rectitude characterized the immediate impact on meeting him. Sympathy, warmth and wisdom were lavished generously on patient or friend.

His place in the history of medicine is assured by genuine scientific achievement based on bedside experience. His numerous publications cover practically every aspect of the cardiovascular system and repeated reference is made to the effects of the thyroid. The subject of the lecture today, "The Heart and the Thyroid; with Particular Reference to I^{131} Treatment of Chronic Heart Disease" seems, therefore, appropriate.

The interrelationship of the thyroid and the heart has enjoyed a long and honorable tradition. Parry's original description of exophthalmic goiter in 1786, published in 1825,[1] is recorded, indeed, as a form of heart disease at the beginning of the chapter entitled "Diseases of the Heart." Parry thereupon describes the clinical manifestations of exophthalmic goiter and their association with congestive failure and angina pectoris in these patients. With the exacerbation of the signs and symptoms of toxic goiter, evidences of congestive failure and/or angina pectoris became more severe. He also notes the parallel subsidence of both groups of manifestations. With the advent of operative treatment, made possible by the work of Billroth[2] and the classic contribution of Kocher,[3] the beneficial effect of thyroidectomy on congestive failure was clearly stated. In the latter part of the nineteenth and the preceding decades of the twentieth century, clinical interest was awakened in various types of thyrotoxicosis, in which several or many

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This work was carried out under a contract between the Office of Naval Research, the Atomic Energy Commission and the President and Fellows of Harvard College. This investigation was also aided by a grant from the United States Public Health Service and by funds of the Patrons of Research, Beth Israel Hospital, Boston, Mass.

of the characteristic features are absent but in which the manifestations of coexistent heart disease are markedly ameliorated or even abolished after appropriate treatment of the thyrotoxicosis.[4] Interest in the subject in this country may be gaged by the fact that the 1932 meeting of the American Heart Association was devoted entirely to a symposium on "The Thyroid Heart."

The effect of the hyperactive thyroid on the cardiovascular system has been studied extensively. Important insight has been gained into the meaning of the signs and symptoms of hyperthyroidism that are commonly attributed to heart disease.

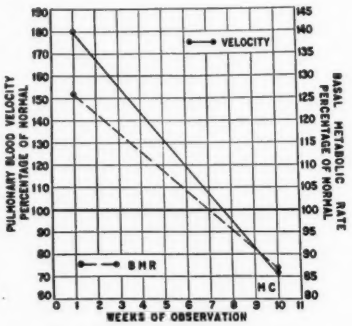

FIG. 1. Relation of the velocity of blood flow through the lungs and basal metabolic rate in patient M. C. Subtotal thyroidectomy was performed during the fourth week of observation.[5]

Velocity of Blood Flow

That the speed of blood flow is increased greatly in thyrotoxicosis was shown in 1927 and 1928.[5] We injected the radioactive deposit of radium emanation, that is, radium C, and, by means of Geiger Counters, measured the pulmonary circulation time. The proportionality between the speed of blood flow and the basal metabolic rate is shown in figure 1.

Minute Volume Output of the Heart

The patient with hyperthyroidism has a greatly increased cardiac output. Recent studies employing the direct Fick principle by means of catheterization show that with increases in the metabolic rate averaging 35 per cent above normal, cardiac output increases 45 per cent above normal.[6] Under such circumstances the cardiac output in thyrotoxic patients at rest corresponds to that of normal individuals doing light work. This increase in minute volume output is accomplished by increasing the number of heart beats, at times by an increase in the output of blood per beat or by a combination of both. The work of the heart is increased not only at rest but even more on effort. Plummer and Boothby,[7] many years ago, observed that a given amount of effort produces a disproportionate rise in output in patients with hyperthyroidism as compared with normal subjects; the "cost of work" is great.

The increased output of the heart in hyperthyroidism evidently serves two main purposes. More blood is supplied to sustain the increased oxygen consumption of the tissues of the body. Also, the body temperature is held constant by a greatly increased blood flow through the skin, with dissipation of the increased heat generated within the body. The internal environment of the body is maintained thereby at a normal temperature. It recently has been shown by Stead and his associates, indeed, that the increased output of the heart in hyperthyroidism is distributed mainly to the skin, muscles and kidneys; the brain and splanchnic area receiving little or no increased blood supply.[6, 8, 9] The blood and extracellular fluid volume is also increased; the increased pulmonary blood volume leads to a diminished vital capacity and dyspnea.[10]

The cardiovascular manifestations of hyperthyroidism are not to be considered merely as an expression of hypermetabolism. The effects of overactivity of the thyroid on other endocrine organs, on many metabolic processes, and on the central and autonomic nervous systems are of unquestionable importance; their exact nature and influence on the cardiovascular system are still imperfectly understood. The increased sensitivity of the thyrotoxic patient to epinephrine is striking. The susceptibility of the heart in hyperthyroidism to develop auricular fibrillation, auricular flutter, and other arrhythmias is well known, occurring in continuous or paroxysmal forms in about 10 per cent of the patients.[11] The responsible mechanisms for these arrhythmias are not wholly clear despite certain classic contributions including those of Nahum and Hoff.[12]

In regard to the tachycardia of hyperthyroid animals, it has been shown that this will persist after the heart has been isolated from the peripheral vascular tree and from all neural pathways. Markowitz and Yater, moreover, showed that thyroxin causes "tachycardia" to occur in fragments of heart muscle removed from two-day chick embryos before any nerve cells within the heart or neural pathways to the heart have been formed.[13] Although the available data are not conclusive as to the precise mechanism by which thyroid hormone affects cellular metabolism, some of the critical enzyme systems are evidently implicated.[14, 15]

The foregoing cardiovascular deviations clarify the meaning of the clinical signs and symptoms of palpitation, tachycardia, increased pulse pressure, and cardiac overactivity with vigorous heart sounds and systolic murmurs. The increased pulmonary blood volume and decreased vital capacity predispose to dyspnea, especially on relatively moderate effort. Slight or moderate cardiac enlargement has been reported in approximately 50 per cent of cases of uncomplicated hyperthyroidism by various observers. In the absence of coexistent organic disease much, if not all, of this enlargement may be due to dilatation. Extreme degrees of cardiac enlargement, rarely if ever occur. When such a finding is encountered, it is usually safe to assume that much of the enlargement has resulted from coexisting nonthyrogenous heart disease.

The fundamental genesis of the exaggerated cardiovascular response in hyperthyroidism presents many gaps in our knowledge. No constant, specific myocardial lesions are found in the hearts of patients who have died of thyrotoxicosis. Varying degrees of lymphocytic infiltrations, spotty degeneration, fibrosis, fragmentation and segmentation of muscle fibers, etc., have been observed, but such changes occur with almost equal regularity in the hearts of patients dying of other causes.

Angina Pectoris and Congestive Heart Failure

Opinions differ as to whether angina pectoris or congestive heart failure ever occur in thyrotoxicosis without coexistent heart disease. Clinically, however, there can be no question but that alleviation of the hyperthyroidism in many instances is accompanied by marked amelioration or even complete disappearance of the angina pectoris and congestive heart failure. Such patients may have a degree of coronary arteriosclerosis or other organic lesions which, by themselves, are insufficient to cause clinical manifestations in the absence of the additional strain imposed by hyperthyroidism. The degree of relief of congestive failure and angina pectoris is so remarkable that "thyroid heart disease" is often classified as one of the "curable" forms of cardiovascular disorders. Congestive failure frequently masks the clinical hallmarks of hyperthyroidism. Particularly in the older age groups, all eye signs, tremor and nervousness may be absent, the thyroid normal in size. The vigorous and roughened first heart sound with apical presystolic murmur and thrill, the systolic murmur, cardiac enlargement, or auricular fibrillation and rapid rate in the presence of congestive failure may lead to an erroneous diagnosis of mitral valvular disease.

The diagnosis frequently will be missed and the crippled cardiac patient will be deprived of his only opportunity of recovery unless we suspect the presence of thyrotoxicosis in one of its manifold manifestations in every cardiac patient and assure ourselves of its presence or absence.

We do not believe elaborate studies are indicated in every cardiac patient. The skillful history and physical examination will provide the clues. Unexplained loss of weight, palpitation, emotional instability, weakness, increased fatigability, increased sensitivity to warmth may be elicited from the patient's history of his illness. Inspection may reveal the flush, a slight stare or minimal exophthalmos, infrequent winking, thyroid enlargement, increased pulsation of the peripheral arteries. Moist warm hands, tachycardia, hyperactive heart sounds, widened pulse pressure, unexplained auricular fibrillation or congestive failure responding unsatisfactorily to digitalis and diuretics call for further exploration of the possibility of thyrotoxicosis. Such definitive studies may include measurement of the metabolic rate, serum protein-bound iodine, and thyroid uptake of tracer doses of I^{131}.

The induction of hypometabolism to alleviate intractable heart disease in patients with normal thyroid function is a natural extension of the favorable cardiovascular effects of lowering the high metabolic rate of thyrocardiac patients to normal. Various circulatory studies lent support to this concept. In patients with congestive heart failure and a normal basal metabolic rate, measurements of the velocity of blood flow had shown considerable slowing; the retardation in the velocity of blood flow generally paralleled the degree of circulatory insufficiency. In patients with myxedema but without congestive failure, "the degree of

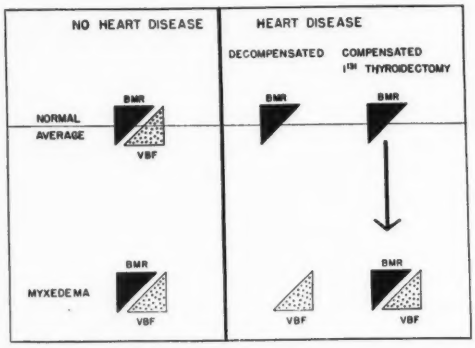

FIG. 2. Relationship between the basal metabolic rate (black areas) and the velocity of blood flow (stippled areas).

slowing was striking, being almost as great as that observed in patients with rheumatic valvular heart disease and auricular fibrillation, who had previously suffered from severe circulatory decompensation and showed symptoms or signs of congestive failure at the time of test. . . . The fact that the myxedematous patients showed no evidence of circulatory insufficiency with a speed of blood flow approximately the same as that of the latter group again emphasizes the fact that the question of whether a given speed of blood flow is adequate can be decided only in relation to the metabolic needs of the tissues."[16] It was, therefore, considered that "if the normal metabolic rate of the patient with congestive heart failure (or angina pectoris) was reduced, his blood supply, while not necessarily altered, might nevertheless be sufficient for the lowered needs of the body."[17] The metabolic demands would be reduced to a level to conform to the blood supply (fig. 2).

SURGICAL TOTAL THYROIDECTOMY

The validity of this hypothesis was confirmed by the results obtained following surgical total thyroidectomy in over 350 patients with intractable angina pectoris or congestive failure operated upon in 26 different clinics.[18, 19] More than 50 per cent of the patients obtained distinct relief of angina pectoris or congestive heart failure and a definite correlation was observed between the degree of induced hypothyroidism and clinical improvement. The magnitude of the operation in these patients with advanced heart disease and the occurrence of surgical complications and progression of the underlying disease, which prevented worthwhile results in approximately one half of the patients, precluded adoption of the procedure as a generally applicable practical measure.

MEDICAL TOTAL THYROIDECTOMY

Following the demonstration of the therapeutic benefit of the thiourea derivatives in thyrotoxicosis, these agents, including propylthiouracil have been utilized in euthyroid patients with angina pectoris or congestive failure in order to attain the hypometabolism of total thyroidectomy. Favorable effects have been reported by certain observers.[20-25] Unfortunately, however, hypothyroidism can be induced in only some patients. Moreover, to maintain the hypothyroid state, administration of the drug must be continued for the remainder of the patient's life. At any time during such administration, dangerous drug reactions, including granulocytopenia, agranulocytosis and death may suddenly occur.[26-32]

The availability of radioactive iodine (I^{131}) led us to investigate its possible use to produce hypometabolism in euthyroid cardiac patients. Since the beginning of our investigation, four years ago, in March 1947, our efforts have proceeded in four main directions: (1) the clinical appraisal of the therapeutic value of the procedure; (2) study of possible deleterious radiation effects; (3) establishment of criteria

for the proper selection of patients; (4) investigation and control of the secondary consequences of the hypothyroid state.[33-35]

In the appraisal of therapy of angina pectoris and congestive failure, it is necessary to bear in mind that the clinical course is often irregular and characterized by periods of unexpected remission and improvement. We, therefore, have selected only patients who, despite marked restriction of activities for many months or years, showed evidence of continued incapacity after having received all standard forms of therapy and in whom remissions of the disease were absent or who continued to suffer signs and symptoms even during periods of slight remission. In all patients included in this report, reliable information regarding the characteristics and severity of the clinical course was available. Some patients had been observed for years in the cardiac clinic of the Beth Israel Hospital and on the wards; others were referred by physicians who placed their records at our disposal. Each patient was appraised independently by several of us before a decision was reached; in many instances, our appraisal was based on observation and study of the patient, including exercise tolerance[36] and other tests, over a period of many weeks or months before radioactive iodine therapy was instituted. Following the administration of I^{131}, the period of 6 to 26 weeks before the development of definite hypothyroidism served as an additional control period.

Results in 26 Patients with Angina Pectoris Observed 12 to 40 Months After Treatment (Average 24 Months)

The severity of cardiac involvement in these patients is reflected by the fact that 27 attacks of acute myocardial infarction had occurred in these 26 patients prior to treatment (table 1). The etiology of the angina pectoris was coronary arteriosclerosis in all. Arterial hypertension with blood pressures ranging from 160–200/90–120 was present in nine. Three other patients died of probable acute myocardial infarction one to three months after treatment, but before hypothyroidism became evident, and accordingly, have not been included.

In the 26 patients with angina pectoris rendered hypothyroid by I^{131}, the therapeutic result has been decidedly worthwhile in 19. In each instance, the patient has been able to undertake activities which had been impossible for many months or years prior to treatment.

Table 1.—*Summary of Results in 26 Cases of Angina Pectoris and Arteriosclerotic Heart Disease*

I. *Clinical data*	
Ages	38–72 yrs. (av. 57)
Sex: Male	20
Female	6
Duration of angina pectoris	1–18 yrs. (av. 5.6)
Number of prior myocardial infarctions	27
Etiologic basis for angina pectoris	
a. all arteriosclerotic heart disease	
b. patient with serologic syphilis—1	
c. diabetes mellitus—3	
d. arterial hypertension—9	
II. *I^{131} therapy*	
Dose administered—total, each patient	26–206 mc.
Average total dose each patient	78 mc.
Average single dose	29 mc.
Number of patients with hypometabolism	26
Duration of follow-up	12–40 mos. (av. 24)
III. *Therapeutic results*	
Excellent 9 (av. follow-up 27 mos.)	
Worth while 10	
Not worth while 7	

In 9 of these 19 patients, the results have been rather remarkable. Angina pectoris has been abolished or only occasional attacks have occurred despite greatly increased activity. The duration of angina pectoris before I^{131} treatment in these 26 patients was from four months to 15 years and averaged 5.6 years. Four male patients have become gainfully employed whereas prior to treatment they had been largely incapacitated for years because of inability to undertake minimal effort without

symptoms. The following cases are illustrative:

Case 1—Angina pectoris, one year. Status anginosus. Coronary arteriosclerosis. Old myocardial infarction. Myxedema induced by four doses of I^{131} totalling 150 mc.; retention by the body 18 mc. Symptoms of myxedema controlled by 30 mg. thyroid daily. Practically complete disappearance of angina pectoris and patient gainfully employed, working eight hours a day as a laboratory assistant for the past 27 months.*

J. L., a 41 year old man (B.I.H. # 69433), was referred through the courtesy of Dr. J. E. F. Riseman. One year prior to I^{131} therapy, attacks of substernal pressure on exertion and emotion were first noted, and an attack of acute myocardial infarction occurred eight months before treatment. He had been unable to work during the nine months before treatment and had been restricted largely to the house because walking even a hundred feet precipitated an attack. He was awakened from sleep by anginal attacks, often suffering three or four episodes nightly. He noted increasing dyspnea and used two pillows. In the month prior to I^{131} therapy, he had used over 500 tablets of nitroglycerine. During his illness, he had received the following treatment; theobromine sodium acetate, potassium iodide, sedatives, quinidine, atropine; nitroglycerine alone was of slight help. There was no history of arterial hypertension or of rheumatic or syphilitic infection.

Physical examination revealed entirely normal findings. The blood pressure was 110/80. The urine and blood were normal. On x-ray examination, the heart was normal in size and shape. The electrocardiogram showed changes consistent with an old posterior infarct.

Post-treatment Course. On April 27, 1948, he received 29 mc. I^{131}; three additional doses of 43, 39 and 39 mc. were administered on July 23, August 13, and November 22, 1948, respectively. Five weeks after the first dose of I^{131}, definite clinical improvement was noted with disappearance of all but a few attacks of angina pectoris. The serum cholesterol level had risen and clinical signs of hypothyroidism were present. During the next few weeks, angina pectoris reverted to the pretreatment severity and frequency; the basal metabolic rate and serum cholesterol values likewise had reverted toward normal. Additional doses led to hypometabolism, marked improvement, and finally, complete disappearance of angina pectoris. In repeated exercise tolerance tests,[33] 45 to 50 trips were performed without anginal pain; the patient stopped exercise at our request or because of fatigue. Repeated pretreatment exercise tolerance tests averaged 30 trips and were invariably halted because of cardiac pain. He has been gainfully employed, working eight hours a day for the past 27 months, experiences no angina except on very strenuous exertion, and is not troubled by symptoms of myxedema. On a daily dosage of 30 mg. of thyroid, the basal metabolic rate is maintained at minus 25 per cent; the serum cholesterol is 900 mg. per 100 cc.

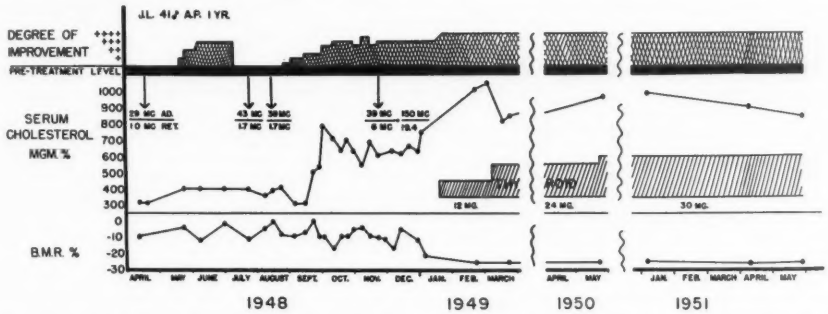

FIG. 3. Case J. L.—The serum cholesterol, basal metabolic rate, and the clinical course following five doses of I^{131} totalling 150 mc.

Case 19—Arterial hypertension. Three prior myocardial infarctions. Angina pectoris for 10 years, severe and disabling for the past nine, markedly restricting activity and requiring frequent nitroglycerine and Demerol for relief. Myxdema induced by six doses of I^{131} totalling 130 mc., with 20 mc. retained in the thyroid. Striking relief of angina pectoris for 12 months despite greatly increased activity. Recurrence of angina pectoris during subsequent 12 months but less severe than before treatment, maintenance of increased activity.

L. A., a 67 year old woman, had had angina pectoris for 10 years, and was referred through the courtesy of Dr. Paul D. White, who had observed the patient for five years. She had suffered three myocardial infarctions eight, five, and one year before I^{131}. During the four years before I^{131} treatment

* The millicurie in these studies conforms to the Bureau of Standards millicurie.

she was largely housebound and suffered attacks daily, not only on effort but on excitement and at night. Despite marked limitation of activity, approximately 60 nitroglycerine tablets and frequent injections of Demerol were required each week.

On physical examination, the heart was enlarged to the left; the rhythm was regular; soft apical and basal systolic murmurs were audible. The blood pressure was 164/92. A small nodule was felt at the right lower pole of the thyroid. The basal metabolic rate was −5 per cent and the serum cholesterol 425 mg. per 100 cc. Electrocardiogram showed left bundle branch block.

I¹³¹ treatment was begun on April 18, 1949. Four doses totalling 84 mc. were administered. Striking improvement manifested by freedom from angina a basal metabolic rate of −20 per cent, a serum cholesterol level of 350 mg. per 100 cc. and has not been troubled by symptoms of hypometabolism during the post-treatment period of 39 months. He has been gainfully employed as a foreman of bricklayers, work requiring considerable physical activity, for one year. Similar striking results have been obtained in six other patients.

In the remaining 7 of the 26 patients with angina pectoris, the therapeutic result has not been worthwhile. Two of the seven patients died, 12 and 19 months after receiving treatment with I¹³¹ (cases 10, 11). In one case (case 8), angina pectoris was relieved for six months

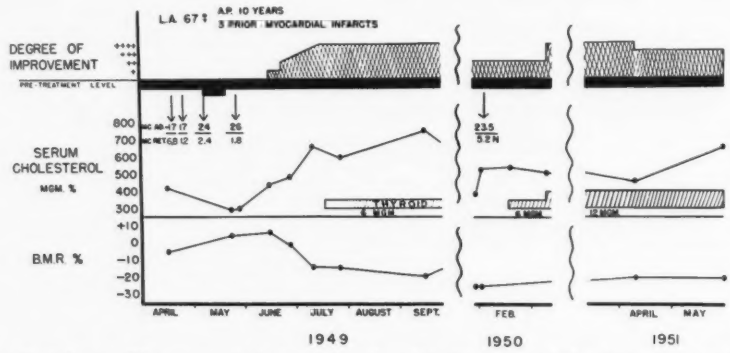

FIG. 4. Case L. A.—The serum cholesterol, basal metabolic rate, and the clinical course following administration of I¹³¹.

pectoris despite increased activity was first noted 10 weeks after treatment and was maintained 14 months. Two additional doses totalling 46 mc. were administered when hypometabolism diminished. The basal metabolic rate has been maintained at −20 per cent; the serum cholesterol at approximately 460 mg. per 100 cc. On 12 mg. of thyroid daily, she experiences only slight discomfort from the hypometabolic state. During recent months the clinical course has been uneven. She has experienced no attacks for weeks and at other times, especially when under emotional stress, has had as many as five attacks daily. At no time have the attacks been as severe as before treatment. She has been able to maintain a level of activity considerably above that before I¹³¹ treatment.

Another patient, R. A., 62 years of age, a bricklayer, had had severe angina pectoris for three years and had been invalided at home since acute myocardial infarction and pulmonary edema 14 months before treatment. He suffered frequent attacks of paroxysmal nocturnal dyspnea. Following three doses of I¹³¹, myxedema was produced with complete remission of all cardiac symptoms. He has been maintained on 30 mg. thyroid daily at but has relapsed to pretreatment status. In the other four patients, the results were unsatisfactory.

THE EFFECT OF HYPOTHYROIDISM ON CONGESTIVE HEART FAILURE, PAROXYSMAL NOCTURNAL DYSPNEA AND PULMONARY EDEMA

Thirteen of the 39 patients were incapacitated primarily because of congestive heart failure (table 2). In six patients the results have been worth while; in seven they have not been worth while. The duration of the worthwhile improvement in the six patients has been 9 to 35 months to date (average 20 months). In four, the improvement has been striking. The relief from dyspnea, attacks of pulmonary edema and paroxysmal nocturnal dyspnea has been associated with objective evidences of diminution or disappearance of peripheral edema and of pulmonary congestion. In patient

M. G., orthopnea and ascites have disappeared, the liver is no longer palpable, cyanosis has disappeared and the vital capacity of the lungs has increased from 2,200 cc. to 3,650 cc. Incapacitated for one and one-half years before treatment, the patient has been able to engage in useful activity during the past 26 months.

Four patients with congestive failure have died, one patient after showing definitely worthwhile improvement for 20 months. The other three patients died, 2, 4, and 18 months after the induction of hypothyroidism without significant improvement.

TABLE 2.—*Summary of Results in 13 Cases of Congestive Heart Failure*

I. *Clinical data*	
Ages	31–70 (av. 49)
Sex: Male	6
Female	7
Rheumatic heart disease	8
Hypertension: arteriosclerotic heart disease	5
Prior myocardial infarctions	3
Duration of congestive failure	6 mos.–17 yrs. (av. 5 yrs.)
II. *I^{131} therapy*	
Dose administered—total, each patient	25.5–125 mc.
Average total dose, each patient	61 mc.
Average single dose	26 mc.
Follow-up	5–37 mos. (av. 20)
III. *Therapeutic results*	
Excellent (av. follow-up 25 mos.)	4
Worth while	2
Not worth while	7

In addition to the foregoing 13 patients, symptoms and signs of congestive failure were present in many of those incapacitated primarily because of angina pectoris; significant improvement in angina pectoris was associated with comparable improvement in the manifestations of congestive failure, the signs and symptoms being impressively relieved or entirely dissipated. The following cases are illustrative:

Case 15. Hypertensive and arteriosclerotic heart disease. Two previous attacks of acute myocardial infarction seven and five years before I^{131}. Chronic renal disease with one remaining kidney. Chronic severe congestive heart failure. Auricular fibrillation. Myxedema induced by two doses of I^{131} totalling 57.5 mc. with marked improvement for 30 months in all manifestations of congestive failure. Amount retained in body 39 mc. A striking therapeutic result.

Pretreatment History. M. G., a 44 year old male and a former automobile mechanic (B.I.H. # M1759), had had arterial hypertension for nine years, and had had two prior attacks of acute myocardial infarction. One and a half years before treatment, ankle edema and dyspnea appeared, the blood pressure was 230/120, a nonfunctioning kidney was demonstrated and a left nephrectomy was performed. The blood pressure was reported to have dropped to 114/70. Five months before entry he noted recurrence of ankle edema, increased weight and dyspnea. Despite a low-salt diet, digitoxin and mercurial diuretics, the dyspnea, orthopnea and intermittent edema became worse and he was hospitalized. On vigorous treatment with bed rest, low-salt diet, a period on a rice diet, digitoxin, supplementary vitamins and frequent injections of mercurial diuretics as well as thoracenteses, the patient improved only slightly during seven weeks of hospitalization.

Pretreatment Physical Examination. The patient was dyspneic, orthopneic and slightly cyanotic. The salient findings were as follows: blood pressure of 130/80, distended neck veins, signs of right hydrothorax; with moist rales at both bases, marked enlargement of the heart, grossly irregular rhythm, a grade I apical systolic murmur, protuberant abdomen. The liver was firm, nontender and enlarged five fingerbreadths below the right costal margin. The splenic tip was palpable. Pitting edema over the sacrum was 2 plus, and over the ankles, 1 plus.

Pretreatment Laboratory Examination. The urine specific gravity was 1.019, with 2 to 4 plus albumin; the sediment showed 1 to 10 white cells, occasional erythrocytes and fine granular casts. Blood was normal except for the nonprotein nitrogen which was 54 mg. per 100 cc. Electrocardiograms showed auricular fibrillation and evidence of old posterolateral infarction and left ventricular hypertrophy.

Post-treatment Course. On October 12 and October 23, 1948, the patient received 27 mc. and 30.5 mc. I^{131}, respectively, and retained 39 mc. in the body (fig. 5). For two months after treatment, he remained seriously ill with no significant change in his congestive failure. At the beginning of the third month post-treatment, the evidences of hypothyroidism, including a rise in the serum cholesterol occurred, and he exhibited progressive improvement.

During the past 30 months, he has been able to

undertake considerable activity, including doing some carpentry and considerable walking, without developing dyspnea. Orthopnea requiring six to eight pillows disappeared and is no longer present. He now sleeps on one pillow. The patient states that he has not felt this well since several years prior to treatment. Venous distention has disappeared and there is no peripheral edema. Lungs are clear to percussion and auscultation. Ascites, present at the time of treatment, did not recur after one paracentesis. Neither spleen nor liver is now palpable. The electrocardiogram is unchanged. Venous pressure has been 100 mm. of water (compared to 260 mm. before treatment), vital capacity 3,300 cc. (compared to 2,200 cc. before treatment), and the arm-to-tongue circulation time 30 seconds. The nonprotein nitrogen has remained approximately 60 mg. per 100 cc. The period of marked and sustained improvement is now 30 months.

Mrs. R. K., 49 years of age, was referred to us in 1949 for radioactive iodine treatment by Dr. Paul D. White. She had had acute rheumatic fever at 13 with subsequent aortic and mitral valvular involvement. There was progressive loss of functional reserve requiring termination of second pregnancy at 29 years of age, 20 years before the present admission. During the four years before treatment she had had cough, dyspnea, orthopnea, ankle edema, episodes of paroxysmal nocturnal dypsnea, and pulmonary edema despite repeated injections of mercurial diuretics, salt-free diet, digitalis, ammonium chloride. She had been confined to a bed-and-chair existence and required oxygen therapy intermittently. On hospitalization elsewhere under the care of Dr. White, her congestive failure had been refractory to all medical measures.

Physical Examination. The patient was a thin, fairly well-developed woman with moist rales at the right base, heart enlarged to the anterior axillary line, physical signs of mitral and aortic stenosis and insufficiency, hepatomegaly four fingerbreadths below the right costal margin, liver tenderness, moderate sacral, ankle, and pretibial edema. Laboratory examinations showed albuminuria, vital capacity 1,500 cc. and basal metabolic rate minus 2 per cent.

The diagnoses were: chronic congestive failure; rheumatic heart disease; aortic and mitral stenosis and insufficiency; auricular fibrillation.

On the eleventh, eighteenth, and twenty-eighth hospital days she received 20, 15, and 25 mc. of I^{131} respectively with retention of 35, 8, and 2 per cent in her thyroid gland after 24 hours. She was discharged on the thirty-first hospital day.

Dr. Paul D. White, who has observed the patient during the two years since treatment, states that she has shown evidences of congestive failure only occasionally, requires mercurial diuretics once a week, and has lost the edema of her legs. The vital capacity has increased to 1,800 cc. She has been able to be up and around outdoors and not infrequently goes to theater or dinners. She takes daily doses of thyroid, alternating between 12 and 18 mg. ($\frac{2}{10}$ and $\frac{3}{10}$ grains). Dr. White has expressed the following opinion: "I believe that Mrs. K. has been a striking success of irradiated iodine therapy in the control of her congestive heart failure. She has survived two years despite a good deal of strain. I am convinced that she would have died at least a year and a half ago if she had not had irradiated iodine therapy."[37]

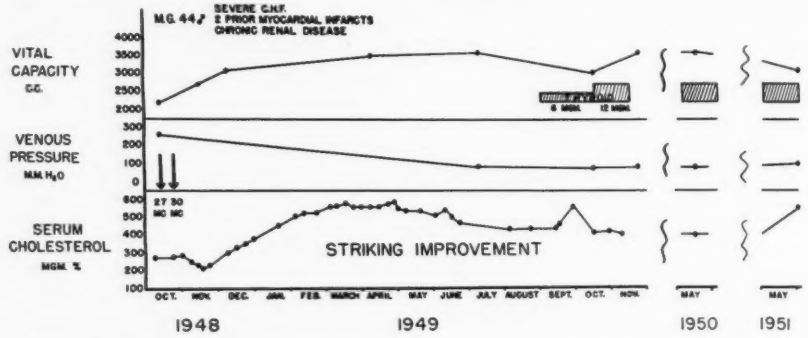

FIG. 5. Case M. G.—The vital capacity, venous pressure, and serum cholesterol following administration of I^{131}.

DISCUSSION

Possible Toxic Radiation Effects

Throughout our investigation, we have been concerned with possible adverse radiation effects. Before the therapeutic studies of the present communication were undertaken, ob-

servations were made with gradually increasing doses in euthyroid patients in terminal state. The results of these studies indicated that persistent hypothyroidism could be induced by one or more appropriate doses.[33-35] Radiation sickness has not been observed in any patient in our series. Similarly, extensive examinations of the blood, urine, liver, and kidney function, have revealed no toxic effects. The distribution of radio-iodine in organs other than the thyroid has been studied and histologic examinations carried out in a smaller series of patients have been in accordance with the above findings and with the data of others.[38-41]

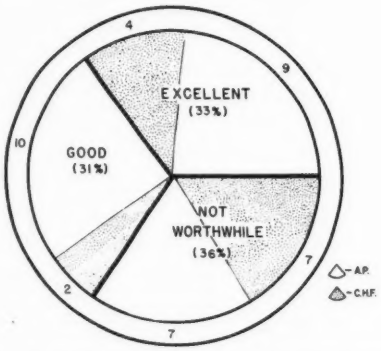

FIG. 6. Results in 39 euthyroid patients with angina pectoris and congestive failure treated with I^{131}.

General Appraisal of Results

Each of the patients selected for treatment had received all the conventional medical measures, and, nevertheless, had remained incapacitated for months or years. While unexpected improvement in such patients occasionally occurs, the rather remarkable improvement observed in approximately one third of all patients treated, and the satisfactory improvement experienced by another third of the patients has been impressive (fig. 6).

It was of considerable interest to observe the relation between clinical improvement and the occurrence of hypometabolism. The irregular interval of five weeks to six months after I^{131} treatment, before hypothyroidism becomes evident, is a helpful safeguard against the possible confusing effect of suggestion. Neither physician nor patient can foretell the time at which hypometabolism and clinical improvement will occur. The clinical improvement, first noted by the patient and later found to be coincident with the inception of hypometabolism when the results of the serum cholesterol and basal metabolic determinations are made available, is consequently the more impressive. Conversely, some patients who showed thyroiditis one to two weeks after I^{131}, with pain, tenderness, and increased heat over the thyroid area, noted that their condition was definitely worse. In some of these individuals the basal metabolic rate had increased slightly and the serum protein-bound iodine had risen. The correspondence between metabolic levels and clinical cardiac status was observed on 31 occasions in the first 23 patients treated.

Selection of Cases for Treatment

This method of treatment is not advised for most patients with angina pectoris and congestive failure. For most patients with angina pectoris and congestive failure, medical treatment successfully alleviates discomfort and provides increased capacity for a satisfactory program of life. In some patients, rapid progression of disease or complications such as acute myocardial infarction or embolic phenomena terminate life after a relatively brief intermediate period of severe discomfort or marked restriction of activity.

There is, however, a relatively small group of patients with angina pectoris or congestive failure, who remain incapacitated and in great discomfort despite all available measures. The disease process is apparently relatively stationary for months or years; the patients enduring great discomfort from congestive failure, or numerous attacks of angina pectoris daily, despite all medical measures. For these patients afflicted with severe angina pectoris, various surgical measures such as sympathectomy, posterior rhizotomy, omentopexy, pericoronary neurectomy, have been advised. For some of these patients radioactive iodine therapy offers the possibility of considerable improvement without the pain and the inevitable hazards of surgery.

Although it is too early to formulate final

indications and contraindications, it is nevertheless desirable to offer a tentative opinion regarding the criteria for the proper selection based on our experience in these 39 patients observed after treatment, on the average, for 23 months.

Unfavorable factors which incline us to advise against treatment may be summarized as follows:

1. *Rapidly progressive cardiovascular disease* (malignant hypertension, syphilitic cardiovascular disease). There is no reason to believe that hypothyroidism retards the progression of the underlying pathologic process. Even though the patient may experience improvement for a few weeks or months after treatment, a relapse to his former clinical condition is likely to occur if a rapidly advancing pathologic process underlies his difficulties. It is also unwise to treat patients who are in the terminal phases of their disease, particularly since five weeks to six months intervene before the hypometabolic state is attained. However, the presence of moderate or even marked hypertension does not contraindicate the treatment.

2. *Hypothyroidism; low basal metabolism.* The presence of pre-existing hypothyroidism represents a contraindication to treatment. Patients with a basal metabolic rate of −15 per cent or lower, while they may be relieved of their symptoms when myxedematous at −35 or −40 per cent, often suffer a recurrence of their symptomatology when maintained at the necessary level of −20 to 25 per cent, which is only slightly below their pretreatment level.

3. *Associated conditions.* The presence of other conditions which may incapacitate the patient and becloud evaluation of this method of treatment constitutes a contraindication. These include active infection such as rheumatic fever, bronchiectasis, emotional instability, cirrhosis of the liver and recent acute myocardial infarction. Intermittent claudication is not benefited by the induction of hypometabolism; on the contrary it may be aggravated and constitutes a definitely unfavorable factor. Similarly, the symptoms of severe painful hypertrophic arthritis may be aggravated.

Favorable Factors. Patients who may be expected to gain the greatest benefit are those in whom the disease has been relatively stationary or only slightly progressive over a period of one or more years. Even though such patients may be seriously incapacitated and may have angina pectoris at rest in bed, if their condition has been quite stable over a period of three months or more, a favorable response to this treatment is likely. Patients with congestive failure should show evidence of some cardiac reserve, such as ability to lose the signs of congestive failure on rest in bed or with the use of diuretics and digitalis. The basal metabolic rate should be above −15 per cent. It is also important that the patient be alert, cooperative and emotionally stable.

When patients are frankly myxedematous with basal metabolic rates of −30 to −40 per cent they are often irritable and nervous. On receiving small doses of thyroid to maintain them at a level of −15 to −25 per cent, they are frequently more stable emotionally than before treatment, and mentally as acute as formerly. In an occasional patient, such as J. K., this factor may be significant; the patient stating that all his life prior to treatment he was prone "to fly off the handle whereas now I am more even-tempered." The precise mechanisms responsible for these effects are not clear though the adrenal and other endocrine organs may well be involved.

Program of I^{131} Treatment

Our present program of treatment entails the following measurements and observations: in every instance tracer doses of 100 to 150 μc. of I^{131} are administered. On the basis of uptake measurements an initial dose of 20 to 30 mc. is given, which delivers approximately 40,000 equivalent roentgens.

Following the administration of the therapeutic dose, similar measurements by direct counting are made of the uptake of the therapeutic dose by the thyroid 24, 48, and 72 hours after its administration to ascertain the amount of the therapeutic dose retained in the thyroid. It is, of course, imperative to instruct all patients regarding the safety precautions relative to contamination of clothing and skin, storage of urine immediately following the

therapeutic dose, and other necessary safeguards. Although approximately two-thirds of the patients have exhibited mild to moderate thyroiditis lasting 1 to 10 days after therapy, it has been severe in only one instance. No treatment except the use of analgesics has been indicated. Inasmuch as thyroid hormone is apparently released during the stage of thyroiditis, the activities of the patient should be reduced to a minimum during this time.

In our experience hypometabolism has developed five weeks to six months following an adequate dose of I^{131}. When patients do not develop hypometabolism within several months, it has been our practice to administer additional doses after preliminary tracer dose studies to determine whether residual thyroid tissue capable of taking up I^{131} exists. In a significant proportion of patients additional doses of I^{131} are necessary. As many as four and five doses at various periods of time have proved to be necessary, but in each instance myxedema was finally achieved.

A simpler program of treatment has been employed by Wolferth and his associates with apparently successful results.[42] They have administered a single dose of approximately 10 to 20 mc. after preliminary tracer doses. This has resulted in a satisfactory depression of thyroid function in many of their patients. Some of these patients have been maintained without additional doses of I^{131} and have required no thyroid medication. Others have required additional doses of I^{131}. If troublesome symptoms of hypothyroidism or myxedema ensue, 6 to 30 mg. of thyroid substance are administered daily. Jaffe and his associates[43] at the Cedars of Lebanon Hospital, Los Angeles, have administered a dose of approximately 6 mc. each week for five weeks. Two months after completion of the first course of 30 mc., the patient is re-evaluated. If there has not been sufficient improvement, and if the patient is not hypothyroid, a second course of weekly treatments is given. The patient is re-evaluated after two months and, if necessary, a third course is given. The relative merits of these programs must await the results of extensive experience.

Repeated administration of I^{131} is particularly indicated when thyroid adenomata are present. In some patients, these adenomata are plainly evident at the time of initial examination. In others they have become apparent only after the normal thyroid has disappeared following the first one or two doses of I^{131}. Presumably these nodules are initially nonfunctioning and do not take up I^{131} until the normal thyroid tissue has been destroyed. The adenomata apparently then begin to function and may be affected by subsequent doses of I^{131}. Subsequent doses are frequently followed by tenderness of the nodule, its gradual disappearance, and the induction of myxedema with its characteristic clinical manifestations.

It has been our practice to permit marked hypothyroidism or, in some instances, even complete myxedema to develop to assure ourselves that all thyroid tissue has been affected and then to give 6 or 12 mg. of thyroid ($\frac{1}{10}$ to $\frac{2}{10}$ grain) daily. In each patient, thyroid dosage has been adjusted to maintain the patient at the lowest metabolic level at which he experiences the maximum relief from his cardiac disease and the minimum discomfort from myxedema. In certain individuals this may not be possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid is administered to obviate the discomfort of myxedema. Most patients are maintained at a basal metabolic level of approximately -20 to -25 per cent on a daily dosage of 6 to 30 mg. thyroid.

Occasionally patients may suffer a recurrence of their symptoms due to the fact that residual thyroid tissue has regenerated with return of the metabolic rate to pretreatment levels. In such instances, thyroid is withdrawn and if tracer doses show uptake of I^{131}, an additional therapeutic dose is administered.

In addition to these special considerations, the same careful supervision and therapeutic program indicated in all patients with heart disease is essential. The radioactive iodine treatment of heart disease is not to be considered as curative; it is a palliative procedure which is to be considered as an adjunct to the recognized medical measures.

Hypercholesterolemia, Myxedema, and Arteriosclerosis

The question naturally arises as to whether the induced high cholesterol values and hypothyroidism dispose these patients to an increased progression of arteriosclerosis. In our patients, the situation is not strictly analogous to untreated complete myxedema, since our patients receive small doses of thyroid. In this connection we have reviewed the clinical course and postmortem findings of a group of patients who survived 1 to 11 years following surgical total thyroidectomy, and in whom hypometabolism with elevated cholesterol values was present.

We have been interested particularly in the younger patients with rheumatic heart disease. In them, only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed postmortem in such patients, the lesions might well be attributed to the myxedematous state. In all five such patients who survived 1 to 11 years in the hypothyroid state after surgical total thyroidectomy, careful postmortem studies by the Schlesinger technic have revealed only minimal or no coronary arteriosclerosis. Although the number of patients is small, these results demonstrate that progressive arteriosclerosis of the coronary arteries is not a necessary concomitant of the hypercholesterolemia of hypothyroidism or of the hypothyroid state. Because of the above considerations and the uncertain etiological relation of the elevated cholesterol and blood lipids of hypothyroidism to atheromatosis, we have not considered pretreatment elevation of serum cholesterol levels, a contraindication to therapy of these disabled cardiac patients.

The Question of "The Myxedema Heart"

As in previous studies, particular attention has been devoted to the appearance of evidence of the signs or symptoms of the so-called "myxedema heart."

An increased cardiac silhouette or area of percussion dullness, decreased voltage of the electrocardiogram and less forceful pulsations on fluoroscopy have been observed in some of our subjects. But "myxedema heart" in the sense of a condition aggravating or precipitating attacks of angina pectoris or congestive failure did not develop. On the contrary, with the appearance of such changes, striking clinical improvement has been witnessed. In some patients with congestive failure, the cardiac silhouette becomes smaller, the disappearance of the dilatation of the failing heart offsetting the effect of myxedema on the heart. Our experience is consequently in accordance with that of Willius and Haines,[44] Means, White and Krantz[45] and Christian,[46] who concluded that "myxedema heart" in the sense of causing heart failure occurs rarely, if at all.

Results of Others

The experience of others in the treatment of intractable heart disease is confirmatory of our own results. Wolferth, Chamberlain and Mead have recently reported their observations on 28 euthyroid patients followed for 6 to 24 months after treatment.[42] All had extremely severe angina pectoris and had shown no improvement or become worse despite conventional methods of treatment. In the majority of patients, the most serious problem was nocturnal seizures frequent enough to make adequate rest impossible. Many had suffered one or more attacks of myocardial infarction. Six others had aortic valvular disease with great enlargement of the left ventricle. At least nine had experienced congestive failure and most of these had congestive failure at the time I^{131} was administered. Nine had fairly severe hypertension. The authors state: "Because the treatment was administered only to patients with far-advanced disease and was denied to none in whom even a remote possibility for relief was thought to exist, it was anticipated we would encounter many cases in which no improvement would result and that a high mortality would be experienced within a short period of time." As anticipated, 10 patients died, six of them less than a month after treatment before the hypothyroid effect of I^{131} could be exerted. In the remaining 18 cases, the results were judged to be good in 12, fair in four, and in two, unsatisfactory. A summary of their results is presented in the accompanying table (table 3). The authors express their judgment

as follows: "Although large doses of radioactive isotopes should not be used indiscriminately, our experience during the past two years in deliberately depressing normal thyroid function has convinced us that radioactive iodine has a place in the treatment of severe, otherwise intractable angina pectoris, as well as certain cases with severe congestive failure or abnormal cardiac mechanisms with poorly controlled tachycardia. . . . Radioactive iodine in appropriate dosage is capable of relieving otherwise intractable severe anginal pain."

TABLE 8.—*Summary of Results*[42] *in 28 Patients with Angina Pectoris Treated with* I^{131}

28 Patients—Angina Pectoris
Follow-up 6–24 months
Cong. fail., 9; art. hypert., 9
10 Died
6 d. less than 1 month
3 d. sev. mos., striking imp. A.P.
1 d. after sl. imp. one year
18—Follow-up 6–24 Mos.
12 good
4 fair
2 unsatisfactory

TABLE 4.—*Results of 95 Patients with Angina Pectoris and Congestive Failure Treated by Jaffe et al., Cedars of Lebanon Hospital, Los Angeles*[43]

Ang. Pectoris and Cong. Failure, 95 Patients

	A.P.	C.F.	A.P. & C.F.	Totals	
Good	15	15	23	53	= 56%
Fair	10	6	8	24	= 25%
Poor	3	3	1	7	18 = 19%
Deceased	1	8	2	11	
Totals	29	32	34	95	=100%

In a personal communication, Dr. Henry L. Jaffe, Director of the Department of Radiation Therapy at the Cedars of Lebanon Hospital, Los Angeles, has kindly permitted us to state the results obtained by him and his associates in treating their first 95 severely ill cardiac patients.[43] Their results are summarized in the accompanying table (table 4). They have used the divided dose technic and have not attempted to treat all patients to the point of actual clinical myxedema unless they failed to achieve maximum clinical improvement with smaller doses. "Altogether," he states, "we are satisfied that this form of treatment offers something for the severe cardiac which was not available before."

Reports of results in a few cases have been made available to us from several clinics, but while encouraging, the experience is too fragmentary to permit evaluation.

Future Studies

Future experience will clarify many aspects of this new form of therapy.

The criteria for the selection of patients with angina pectoris and congestive failure cannot be definitely established until much more experience in various clinics over an extended period of time becomes available. Additional experience will afford information regarding the durability of the beneficial effects and the question as to whether or not life is prolonged. It is, indeed, possible that the elevation of the serum cholesterol and other lipids may accelerate the progress of atherosclerosis although our evidence to date does not support such a conclusion.

Several different schedules of I^{131} administration are already being employed; only extensive trial will clarify the advantages and disadvantages of the various programs of treatment.

Although all studies to date have failed to reveal any untoward radiation consequences, long term observations are clearly indicated. Further studies on the mechanisms by which hypothyroidism achieves its beneficial effect on the circulatory system will be of practical as well as of theoretic interest. The reduction in cardiac work, however important, is probably but one factor. Changes in other endocrine organs as well as in the autonomic and central nervous systems may well play significant roles and are the subject of continuing studies.

SUMMARY AND CONCLUSIONS

1. The physiologic, pathologic, and clinical interrelationships between the thyroid and the cardiovascular system have been discussed.

2. The therapeutic effects of hypothyroidism induced by radioactive iodine in 39 euthyroid patients with intractable advanced angina

pectoris or congestive failure have been described.

3. Only patients were treated who were seriously incapacitated despite all conventional forms of therapy for many months or years.

4. Persistent hypothyroidism can be regularly induced by one or more appropriate doses of radioactive iodine.

5. No radiation sickness and no toxic effects on the blood, kidneys or parathyroids have been observed. Mild or moderate transitory thyroiditis occurred in approximately one-half of the patients.

6. Twenty-six patients with severe angina pectoris have been treated. The average duration of angina pectoris before treatment was 5.6 years. The average follow-up period after treatment is two years and varies from one year to three years. One third of the patients obtained excellent improvement; in another third the improvement, while less, was distinctly worth while. In the remaining one-third the results were not worth while.

7. Among 13 patients severely ill with congestive failure, approximately one-half have shown worth-while improvement; in four it has been striking. The duration of the worthwhile improvement has averaged 20 months with a range of 9 to 35 months.

8. The results of two confirmatory series of cases similarly treated elsewhere have been reviewed.

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The Action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on the Rhythmic Function of the Heart

By MORRIS H. NATHANSON, M.D., AND HAROLD MILLER, M.D.

The actions of norepinephrine and isopropyl norepinephrine on the rhythmic property of the heart were studied and compared with that of epinephrine. Norepinephrine does not abolish cardiac standstill by carotid sinus stimulation, has no effect on the ventricular rate of heart block and induces a sinus bradycardia. Isopropyl norepinephrine acts similarly to epinephrine in that it abolishes the induced cardiac standstill, increases the ventricular rate of heart block and produces a sinus tachycardia. In the treatment of cardiac arrest, the isopropyl compound appears to possess optimum features as it is very potent in the prevention of cardiac standstill and does not predispose to ventricular fibrillation.

THE PROPERTY of rhythmicity or automaticity, the pacemaking function of the heart, is essential to normal cardiac activity. If a pacemaking mechanism is absent, cardiac or ventricular arrest follows in a heart which may be completely competent in its contractile function. In a previous report[1] utilizing the cardiac standstill induced by stimulation of the carotid sinus in man, it was shown that epinephrine and related compounds were the only substances which increased cardiac rhythmicity. Recently two relatively new epinephrine-like compounds have received considerable attention. They are norepinephrine and isopropyl norepinephrine (Isuprel). Norepinephrine differs from epinephrine in the absence of a methyl group on the terminal nitrogen of the side chain and Isuprel has an isopropyl group substituted for the methyl group of epinephrine.

The recent studies on norepinephrine are an important development in the study of the chemistry and physiology of the sympathetic nervous system. It is now known that the adrenal medulla secretes considerable amounts of the nonmethylated compound.[2] There is also considerable evidence that norepinephrine is an important chemical transmitter of sympathetic nerve impulses.[3] Isopropyl norepinephrine (Isuprel) has recently been introduced as a substitute for epinephrine in the treatment of asthma. This compound differs from norepinephrine and epinephrine chiefly in its vascular effect, producing a vasodilatation and a depressor reaction. In the present study, the action of norepinephrine and isopropyl norepinephrine was observed in (a) patients in whom carotid sinus pressure induced cardiac standstill, (b) patients with complete heart block, and (c) patients with sinus rhythm. The effects of these sympathomimetic compounds were compared with those produced by epinephrine.

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Dr. Nathanson died April 24, 1952.

ACTION ON INDUCED CARDIAC STANDSTILL

Norepinephrine was administered to six patients with a hyperactive carotid sinus cardioinhibitory reflex. Levo-norepinephrine hydrochloride was used in all cases. The procedure was as follows: an electrocardiogram was first made to record the induced cardiac standstill. A blood pressure reading was also made at this time. Levo-norepinephrine hydrochloride, 0.03 mg., was then administered rapidly by intravenous injection and blood pressures recorded and electrocardiograms made with carotid sinus compression at one-minute intervals. Following the administration of the drug, there was an abrupt rise in blood pressure which ranged from an increase of 30 mm. systolic and 10

mm. diastolic to 100 mm. systolic and 30 mm. diastolic. The duration of the pressor effect varied from five to eight minutes. Pressure on the carotid sinus consistently reproduced the standstill following the administration of the norepinephrine.

In a previous study,[4] it was shown that Isuprel in doses of 0.14 to 0.2 mg. subcutaneously consistently abolished the cardiac standstill which could be induced by carotid sinus pressure. It was considerably more potent than epinephrine in this respect. In the present study, Isuprel was administered intravenously to six patients in whom cardiac standstill could be induced. The dose was 0.02 mg. After the administration of the drug, the standstill was prevented in each instance. Isuprel consistently produced a drop in diastolic pressure but systolic pressure was not significantly modified.

When compared with the action of epinephrine on the carotid sinus standstill as observed in previous studies[1] Isuprel showed the following differences: (a) Isuprel did not produce a pressor effect, (b) Isuprel was more potent in its action, and (c) it prevented the standstill by restoring the activity of the sinus node or by initiating rhythmic foci in the auricles or high in the ventricles. Epinephrine more frequently abolished the standstill by stimulating lower ventricular foci.

Action of Norepinephrine, Epinephrine and Isopropyl Norepinephrine on the Ventricular Rate of Heart Block

Effects of Intravenous Administration of the Three Substances

The effect of an intravenous injection of the three compounds was studied in eight patients with complete heart block. Levo-norepinephrine and synthetic levo-epinephrine were administered in doses of 0.03 mg. by rapid injection and the dose of Isuprel was 0.02 mg. The smaller dose of Isuprel was used because, in an earlier study, the activity of Isuprel appeared to be greater than that of epinephrine. The procedure was as follows: A control electrocardiogram was made and the blood pressure recorded. The compound was then injected and a continuous electrocardiogram made. The blood pressure was recorded at 30 seconds and thereafter at one-minute intervals. The observations were followed for several minutes after the ventricular rate had returned to the preinjection level.

Following the administration of norepinephrine, there was only a slight and very transitory increase in the ventricular rate. There was a return to the preinjection rate usually within one minute. In contrast, there was a definite and sustained rise in the ventricular rate after the injection of epinephrine. Isuprel also induced a sustained increase in the ventricular

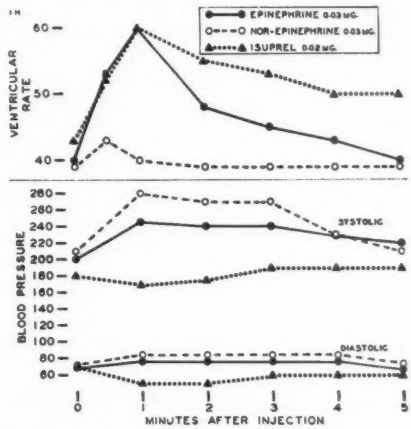

FIG. 1. Patient I. H. Effect of the three compounds on blood pressure and ventricular rate in heart block. Norepinephrine produced the more intense pressor reaction but only a slight and transient increase in the ventricular rate. The nonpressor drug Isuprel induced a sustained increase in the ventricular rate.

rate, which, considering the smaller dose employed, was comparable to that produced by epinephrine. Typical responses of the blood pressure and ventricular rate to these compounds are shown in figure 1. In table 1 is shown the maximum increase in the ventricular rate following the administration of the three compounds. The superiority of epinephrine and Isuprel is considerably greater than is shown in this table, since, as has been mentioned, the ventricular stimulation following norepinephrine was of very brief duration.

In addition to the quantitative variations of ventricular rhythmicity, the drugs appeared to differ in the localization of their effects.

TABLE 1.—*Maximum Increase in the Ventricular Rate (Beats per Minute) in Eight Patients with Complete Heart Block Following the Intravenous Administration of the Three Compounds*

Case	Norepinephrine	Epinephrine	Isopropyl Norepinephrine
1	3	22	16
2	4	20	17
3	3	26	10
4	11	38	20
5	7	29	11
6	9	40	32
7	3	22	28
8	9	47	39

Although norepinephrine showed only a slight and transient action on the basic ventricular pacemaker, it did cause transient excitation of lower ventricular foci resulting in multifocal ectopic beats (fig. 2). This effect was usually observed in the first minute after the administration of the drug. In contrast, the stimulating action of Isuprel was predominantly on the basic pacemaker. Epinephrine also induced ectopic ventricular beats in the early phase of its action. The following observations in a patient with complete heart block suggest that a drug which activates ectopic ventricular foci may produce the serious arrhythmia, ventricular fibrillation.

The patient was a woman, 84 years of age, who entered the hospital because of attacks of syncope and convulsions of two days duration. She was known to have had hypertension for many years and the blood pressure on admission was 240/90. The heart rate was noted to be 40 beats per minute and the electrocardiogram showed complete auriculoventricular block (fig. 3, strip 1). During the first minute after an intravenous administration of 0.03 mg. of epinephrine, many multifocal ventricular premature beats were present (fig. 3, strip 2). On another occasion, the patient received 0.03 mg. of norepinephrine intravenously. Within one minute the electrocardiogram showed a ventricular tachycardia (fig. 3, strip 3), and this passed into a definite ventricular fibrillation (fig. 3, strip 4). The duration of the arrhythmia was about four minutes, when the electrocardiogram again showed complete heart block. On the following day, the patient received 0.02 mg. of Isuprel by vein, which resulted in a definite increase in the ventricular rate arising from a single pacemaker high in the ventricles (fig. 3, strip 5). There was no indication of excitation of lower ventricular centers after the latter.

Effects of Subcutaneous Administration of Epinephrine and Isuprel

Since the usual mode of drug administration in heart block is by subcutaneous injection, the effect of Isuprel, given by this route, on the ventricular rate of five patients with heart

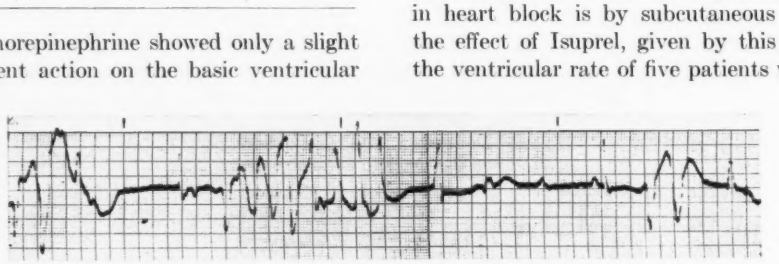

FIG. 2. The induction of multiple ectopic ventricular beats by norepinephrine in a patient with complete heart block.

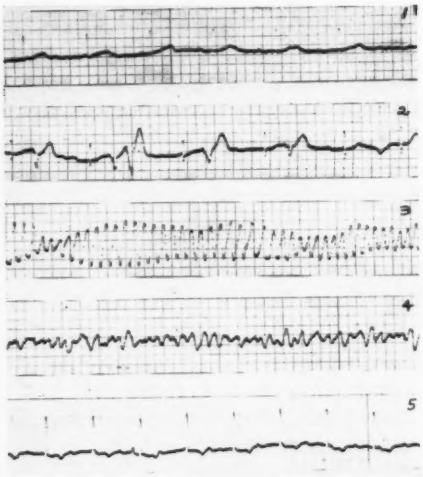

FIG. 3. *Strip 1* is the electrocardiogram of a patient with complete heart block, ventricular rate 40. *Strip 2* shows multiple ectopic ventricular beats during the first minute after an intravenous injection of 0.03 mg. of epinephrine. *Strips 3* and *4* show the development of transient ventricular fibrillation following an intravenous dose of 0.03 mg. of norepinephrine, *Strip 5* shows a ventricular rhythm from a single focus, rate 60, after an intravenous injection of 0.02 mg. of Isuprel. Isuprel induced no ectopic beats.

block was studied. In three patients a comparison was made of the effects of epinephrine and Isuprel. Since our observations on carotid sinus standstill indicated that Isuprel was considerably more active than epinephrine, the dose of Isuprel used was 0.2 mg. and the response compared with that following the administration of 1 mg. of epinephrine. The procedure was as follows: after a control electrocardiogram was made, the drug was administered and electrocardiogram was then made at five-minute intervals for 15 minutes and thereafter at 15-minute intervals. Table 2 shows the results of these experiments. Following the subcutaneous injection of 0.2 mg. of Isuprel, there was a definite and sustained increase in the ventricular rate in each instance. In the three patients in whom both drugs were used, the smaller dose of Isuprel produced a greater effect than the larger dose of epinephrine.

Effect of the Sublingual Administration of Isuprel

The effect of the sublingual administration of Isuprel was observed in four patients with complete heart block. The drug was given to each patient in a 15 mg. dose on one occasion and in a 30 mg. dose at another time. After a control electrocardiogram was made and the drug administered, electrocardiograms were recorded at five-minute intervals for from one to two hours. In two patients, the response to both doses was slight but well sustained (table 3, patients 2 and 4). In two patients, there was a definite sustained increase in the ventricular rate (table 3, patients 1 and 3). The onset of the effect was from 15 to 30 minutes after the administration of the drug and the duration varied from 45 minutes to two hours. The 30 mg. dose produced only a slightly more intense action than did the smaller dose; however, the effect of the larger dose was more sustained. In three of the four patients, a comparison was made of the effects of intravenous and sublingual administration. In two patients, an intravenous dose of 0.02 mg. resulted in a more intense response than that induced by 30 mg. given sublingually. In one patient, the increase in ventricular rate resulting from 30 mg. sublingually was greater than that which followed an intravenous dose of 0.01 mg. The duration of the action following intravenous administration varied from 10 to 15 minutes while the effect lasted up to two hours after the sublingual application of the drug.

TABLE 2.—*Effect of the Subcutaneous Administration of Epinephrine and Isuprel on the Ventricular Rate (Beats per Minute) in Complete Heart Block*

	Patient							
	1		2		3		4	5
	Epi. 1 mg.	Isup. 0.2 mg.	Epi. 1 mg.	Isup. 0.2 mg.	Epi. 1 mg.	Isup. 0.2 mg.	Isup. 0.2 mg.	Isup. 0.2 mg.
Initial Ventricular Rate/Min.	54	54	40	38	47	46	31	20
After								
5 Min.	57	60	41	38	50	50	37	27
10 Min.	61	63	39	43	52	52	48	32
15 Min.	60	60	39	47	52	71	54	45
30 Min.	57	57	42	68	53	65	50	49
45 Min.	60	59	43	60	53	60	46	45
60 Min.		58	41	50	54	54	41	44
75 Min.						55		
90 Min.				38		52		
105 Min.						48		
120 Min.				38		47		
Max. Increase in Vent. Rate	7	9	3	30	7	25	23	29

TABLE 3.—*The Effect of the Sublingual Administration of Isuprel on the Ventricular Rate (Beats per Minute) of Four Patients with Complete Heart Block*

Patient	Dose	Maximum Increase in Ventricular Rate	Duration of Increase in Ventricular Rate
1	15 mg.	32	45 min.
1	30 mg.	47	1½ hrs.
2	15 mg.	5	1 hr.
2	30 mg.	8	1½ hrs.
3	15 mg.	17	1½ hrs.
3	30 mg.	19	2 hrs.
4	15 mg.	3	1 hr.
4	30 mg.	4	1 hr.

ACTION OF NOREPINEPHRINE, EPINEPHRINE AND ISOPROPYL NOREPINEPHRINE ON HEART RATE IN NORMAL SINUS RHYTHM

The effect of the three compounds was studied in eight patients with sinus rhythm. After a control electrocardiogram was made and the blood pressure recorded, the drug was

administered intravenously and a continuous electrocardiogram was made. The dose of norepinephrine and epinephrine was 0.03 mg. and that of Isuprel, 0.02 mg. Blood pressures were recorded at 30 seconds and thereafter at intervals of one minute. Following norepinephrine, there was a transient increase in rate of from 4 to 10 beats per minute, for a period of one minute or less. Following this reaction, there was either a drop in rate to the preinjection level or to a level 2 to 10 beats per minute below the preinjection rate. Following epinephrine, there was a moderate increase in rate of

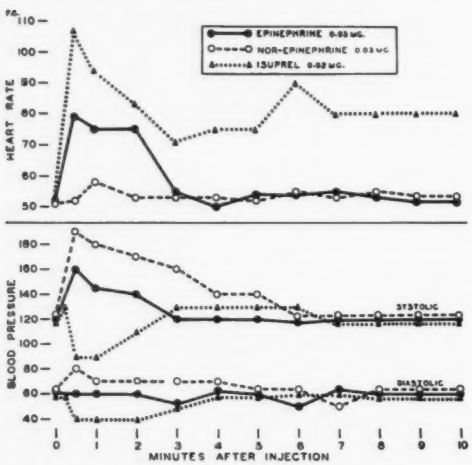

FIG. 4. Patient F. G. Action of the three compounds in a patient with sinus rhythm. Note the marked and sustained tachycardia following Isuprel and the inactivity of norepinephrine on heart rate, although this compound induced the most intense pressor response.

8 and 16 beats per minute in two patients, the reaction subsiding in one minute. In six patients, epinephrine produced a greater increase in rate of from 26 to 67 beats per minute, the tachycardia subsiding usually within two minutes. However, in three patients a rise in rate of from 15 to 30 beats per minute persisted for 10 minutes. The increase in rate following Isuprel was comparable to that induced by epinephrine but was of longer duration. The maximum increase in rate varied from 25 to 62 beats per minute. The period of tachycardia was five minutes in two instances and the duration was 15 minutes or longer in six patients (fig. 4). The blood pressure responses were similar to those observed in the experiments in heart block.

DISCUSSION

The present studies show by several methods that norepinephrine does not have any sustained action on the rhythmic property of the human heart. Isopropyl norepinephrine, although a drug without pressor action, is very potent in its effect on cardiac rhythmicity and appears to act predominantly on higher centers and nodal tissues. Norepinephrine exhibits a transient activation of lower ventricular foci, while epinephrine stimulates both the higher and lower rhythmic centers. The recent studies of Greiner and Garb[5] further indicate that Isuprel is less disposed to produce ectopic rhythms. These observers found that the three compounds increased irritability (lowered the irritability threshold) of heart muscle. Following the application of norepinephrine and epinephrine, automatic rhythm supervened at levels at which the increase in irritability was slight. Isuprel, while affecting a far greater lowering of the irritability threshold, did not produce a corresponding effect on automaticity.

The introduction of a new sympathomimetic compound requires an evaluation of its place in practical therapy and particularly an estimation of its activity as compared with that of epinephrine. In cardiac therapy, the application of the sympathomimetic compounds has been limited almost entirely to the therapy and prevention of cardiac arrest, especially that associated with heart block. The present studies show that norepinephrine has little or no action on the basic ventricular pacemaker and thus would be of no value in the prevention of cardiac standstill. From another standpoint, it is probable that there is a definite danger in the administration of this compound to patients who are susceptible to sudden cessation of cardiac activity. It has generally been supposed that the chief mechanism for the Adams-Stokes syndrome is ventricular standstill. However, it has become increasingly evident that varying degrees of ventricular acceleration and ventricular fibrillation are frequently the basis for this syndrome.[6] Recently

Garb and Chenoweth[7] produced ventricular fibrillation consistently in cats during hydrocarbon inhalation by the administration of norepinephrine and epinephrine while Isuprel did not induce this serious arrhythmia under the same conditions. It is frequently difficult to determine which mechanism, ventricular standstill or fibrillation, is the basis for a sudden cessation of effective cardiac action. If transient ventricular fibrillation is the mechanism, the administration of norepinephrine or epinephrine would tend to perpetuate this arrhythmia, with a possible fatal termination. It is of interest that in the patient described earlier, who was susceptible to the development of ectopic ventricular beats and ventricular fibrillation, Isuprel stimulated only a single rhythmic focus in the ventricles. It would appear that Isuprel possesses optimum features for the prevention and therapy of sudden cessation of cardiac function, in that it is potent in the treatment of cardiac standstill and yet does not dispose to ventricular fibrillation.

There appears to be a difference in the relative potencies of Isuprel and epinephrine, depending on the mode of administration. By the subcutaneous route, on the carotid sinus standstill and on the ventricular rate of heart block, Isuprel is about five times more active than epinephrine. By intravenous administration, Isuprel does not show this degree of superiority. In part, the greater effectiveness by the subcutaneous route may be due to the fact that Isuprel possesses a local vasodilating action in contrast to the vasoconstrictor effect of epinephrine, and thus a more favorable absorption of Isuprel is to be anticipated. For the prevention of cardiac standstill in heart block, drugs are usually administered by the subcutaneous route. The present studies indicate that a dose of from 0.14 mg. to 0.2 mg. of Isuprel will effectively increase the activity of the ventricular pacemaker and thus lessen the tendency to ventricular standstill.

The activity of Isuprel by the sublingual route is of interest in the therapy of conditions in which cardiac standstill may occur, the hyperactive carotid sinus reflex and complete heart block. When attacks are frequent, the patient is usually under observation in a hospital and the drug may be administered by the subcutaneous route. However, in the treatment of patients who are having infrequent attacks and who are ambulant, a drug which can be self administered is desirable. The orally active sympathomimetic compounds, Paredrine and ephedrine may be effective in such instances.[8] The sublingual administration of Isuprel is an addition to the therapy of these conditions by self medication. Our studies indicate that the ventricular rate may be increased by a sublingual dose of 15 mg. of Isuprel. It is suggested that this dose be used three or four times a day or every two hours if indicated.

Conclusions

1. The effects of norepinephrine, epinephrine and isopropyl norepinephrine (Isuprel) on cardiac rhythmicity have been studied by the following methods, (a) the action on cardiac standstill induced by carotid sinus pressure, (b) the response of the ventricular rate of heart block, and (c) the effect on sinus rhythm.

2. As compared with epinephrine and Isuprel, norepinephrine, a potent pressor compound, shows little or no effect on cardiac rhythmicity.

3. Isuprel, having little or no pressor action, produces a potent and sustained increase in rhythmic function.

4. Norepinephrine is of no value in the therapy of cardiac arrest. There may be a definite hazard in the use of this drug in cardiac and vascular conditions because of its disposition to produce ventricular fibrillation.

5. Isuprel appears to possess optimum features for the prevention and therapy of sudden inactivity of the heart in that the drug is very effective in cardiac standstill and yet it does not seem to dispose to ventricular fibrillation.

Acknowledgments

We are indebted to Dr. Gordon A. Alles of Pasadena for the *l*-norepinephrine and to the Sterling-Winthrop Research Institute of Rensselaer, New York, for the synthetic *l*-epinephrine and the isopropyl norepinephrine.

We wish to express our appreciation to Dr. George C. Griffith, chief of the department of cardiology, for his cooperation in this study.

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Hypersensitivity to Mercuhydrin

By JOHN F. WHITMAN, M.D. AND WILLIAM L. PROUDFIT, M.D.

Specific hypersensitivity to the mercurial component of meralluride sodium was induced by a series of intramuscular injections in 12 patients who were being treated for congestive heart failure. Reactions were characterized by fever and systemic symptoms and were precipitated in hypersentitive patients by minute amounts of the drug. No untoward effects resulted from administration of full therapeutic doses of two other mercurial diuretics. Reactions appeared to be modified or inhibited by the action of tripelennamine hydrochloride and British anti-lewisite (BAL); eventual disappearance of the allergic response was demonstrated in two patients.

RECENT ACCENT on the use of mercurial diuretics in the treatment of congestive heart failure has made it increasingly apparent that these preparations occasionally induce unfavorable side effects. The manifestations of toxicity have been attributed, in various instances, to the direct effect of the mercurial drug on the myocardium, to disturbances in water and electrolyte metabolism, to mobilization of digitalis from extracellular fluid, to the protoplasmic toxicity of the mercury ion, and to the specific sensitivity to the material used. Information concerning reactions of an allergic nature[1-16] has been confined largely to isolated reports of cases in which urticaria, erythematous eruptions, exfoliative dermatitis, chills, fever, bronchial asthma, or anaphylactoid collapse occurred after the injection of an organic mercurial compound. The present report concerns 12 patients in whom hypersensitivity to Mercuhydrin (meralluride sodium), manifested by systemic reactions, developed during treatment for congestive heart failure.

MATERIAL AND RESULTS

The age of the 12 patients ranged from 48 to 71 years. Five had arteriosclerotic heart disease, three hypertensive heart disease, and two rheumatic heart disease. A precise etiologic classification was not possible in two cases. The treatment employed included a diet containing not more than 500 mg. of sodium, a fluid intake of 2000 to 3000 cc. daily, adequate digitalization, and daily intramuscular injections of the mercurial diuretic. There was satisfactory diuresis in all patients, and no untoward symptoms were noted for an average of nine days (range 6 to 13 days), by which time an average of 13.5 cc. (range 6.5 to 19) of Mercuhydrin had been administered. Patients were usually free from demonstrable edema prior to the first reaction after having lost 7 to 26 pounds in weight.

In each of the 12 patients, a reaction characterized by fever and systemic symptoms occurred after 6 to 11 injections of Mercuhydrin, and recurred after each subsequent administration of the drug. (See fig. 1.) The temperature rose to an average of 102.6 F., and in each instance returned to normal within 24 hours. The time interval between the injection and the peak of the febrile reaction averaged 6.2 hours. In one case fever was noted within one hour. Eight patients experienced chills, and profuse sweating frequently accompanied the fever. Anorexia was usually present, and five persons reported nausea. Vomiting occurred in three of the latter. Eight patients complained of general malaise and aching in the legs. Transient erythema of the skin most noticeable over the face, neck, and upper trunk appeared in five patients. Three patients had vague anterior chest pain and three others dyspnea. In all instances the symptoms subsided within 12 to 18 hours.

Measurements of the serum sodium in five cases gave normal values in all. The blood urea was measured in seven patients and was found to be elevated in only one. This patient reacted more violently than any of the others.

Minute amounts of Mercuhydrin were given

From the Cleveland Clinic and the Frank E. Bunts Educational Institute. Presented at the twenty-fourth scientific session of the American Heart Association, Atlantic City, N. J., June 1951.

to six patients, 0.05 cc. to five patients and 0.01 cc. to one. In each instance, the resulting reaction was only slightly less severe than that which followed conventional therapeutic doses. The elevation in temperature averaged 101.6 F. and the systemic complaints were the same as in the patients' earlier reactions.

Mercuhydrin is supplied in the form of a sodium salt, each cubic centimeter of which contains 39 mg. of mercury in organic combination with 48 mg. of theophylline. A solution containing 48 mg. of theophylline sodium per cubic centimeter was obtained,* and 2 cc. of this preparation was administered to eight

SUMMARY OF REACTIONS

AGE	49	48	50	57	49	51	58	71	64	61	58	71	AVERAGE
SEX	F	M	F	M	M	M	M	F	M	F	M	F	
ETIOLOGY OF HEART DISEASE	A.S.	R.	R.	H	UNDETERMINED	A.S.	A.S.	H	A.S.	A.S.	UNDETERMINED	H	
MERCUHYDRIN PRIOR TO FIRST REACTION DOSES	6	11	7	10	9	7	8	11	11	7	10	9	9.75
CC.	8.5	13	8.5	16	15	12	15	19	17	9	17	16	13.9
WEIGHT LOSS PRIOR TO FIRST REACTION POUNDS	9	13	7	21	22	12	6	13	23	8	26	20	15.17
DURATION OF TREATMENT PRIOR TO FIRST REACTIONS DAYS	7	13	6	11	8	6	9	10	13	8	9	8	9
TIME FROM INJECTION TO PEAK OF FEVER HOURS	7	5	6	7	7	6	3	7	6	1	9	6	6.2
FEVER F*	103.5	103.3	103	102.6	102.5	102.2	104.3	102.4	101.1	102.2	102	102	102.61
SYMPTOMS DURING REACTIONS													
CHILLS													
MALAISE													
ACHING LEGS													
NAUSEA													
ERYTHEMA													
CHEST PAIN													
VOMITING													
DYSPNEA													
GIVEN THIOMERIN WITHOUT REACTION													
GIVEN THEOPHYLLINE SODIUM WITHOUT REACTION													
GIVEN MERCUZANTHIN WITHOUT REACTION													

A.S. = ARTERIOSCLEROSIS R = RHEUMATIC H = HYPERTENSIVE

FIG. 1. Summary of reactions

patients who had experienced repeated reactions to Mercuhydrin. In none of these did a systemic or febrile response occur.

Mercuzanthine (mercurophylline) was administered by intramuscular injection to three of the patients, and Thiomerin (mercaptomerin sodium) to each of the 12 in doses of 1 cc. or 2 cc. In no instance did a reaction occur.

Fifty milligrams of BAL was given by intramuscular injection to one patient two hours before administering 1 cc. of Mercuhydrin. Mild malaise and nausea were experienced but there was no febrile response. A second patient was given a similar dose of BAL at the same time as the diuretic drug, and no reaction was observed.

One patient was studied again two months after having demonstrated sensitivity to Mercuhydrin and, at that time, 1 cc. of the drug caused a rise in temperature to 102.4 F. On the following day, a similar dose was given and Pyribenzamine (tripelennamine hydrochloride) was administered orally in 50 mg. doses every four hours for four doses, the first dose being given at the same time as the diuretic. The temperature reached a maximum of 99.4 F.

Two patients, each of whom had repeatedly experienced reactions to Mercuhydrin, even in small test amounts, were given gradually

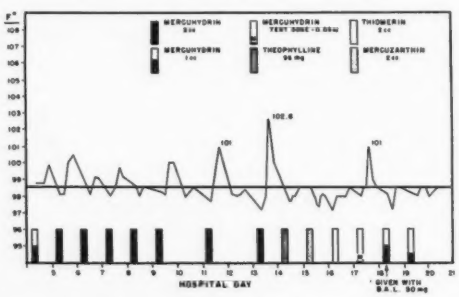

FIG. 2. Case 1. Temperature reactions

increasing doses of the drug 12 months after the original study. Neither experienced a reaction.

CASE REPORTS

The following abstracts of the reactions in three patients are presented to illustrate the phenomenon described and typify the observations made on the other patients in the group.

Case 1. Figure 2 demonstrates the febrile response to Mercuhydrin administered to a 57 year old white man who had severe hypertension, hypertensive and arteriosclerotic heart disease with cardiac enlargement, auricular fibrillation, and congestive failure and who had been experiencing paroxysmal nocturnal dyspnea. The daily temperature was normal prior to the period illustrated in the graph, which begins with the fourth hospital day. Of particular significance are the low grade elevations of temperature following the daily administration of Mercuhydrin prior to the tenth hospital day, at which

* The xanthine component of Mercuhydrin was obtained through the courtesy of the Lakeside Laboratories.

time it was decided to give the diuretic on alternate days. Normal temperature was maintained throughout the tenth and twelfth hospital days, on which no diuretic was given, but significant elevations followed the injections on the eleventh and thirteenth days. On the fourteenth, fifteenth and sixteenth hospital days, the patient received 96 mg. of theophylline sodium, 2 cc. of Mercuzanthin, and 1 cc. of Thiomerin respectively with no reactions. On the seventeenth day, he was given 0.05 cc. of Mercuhydrin, and a fever of 101 F. resulted. On the eighteenth day he received simultaneous injections of 50 mg. of BAL and 1 cc. of Mercuhydrin without subsequent reaction. The next day he was given 0.5 cc. of Mercuhydrin alone and failed to experience a reaction.

Case 2. The patient whose reactions are presented graphically on figure 3 was a 49 year old woman who had arteriosclerotic heart disease with angina pectoris and angina decubitus. During the

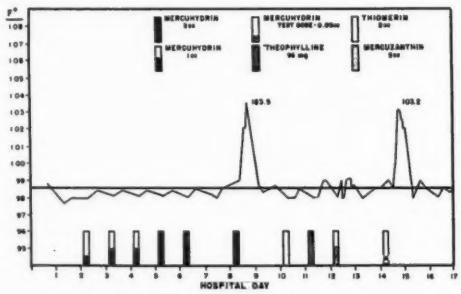

FIG. 3. Case 2. Temperature reactions

first seven days of hospitalization, she was given five doses of Mercuhydrin and no febrile response was noted. Despite the absence of fever, she had experienced ill described discomfort, which included pain in the chest and left shoulder, weakness, and generalized muscular aching, following the last few injections. The patient associated these symptoms with the receipt of the diuretic and refused the medication on the seventh hospital day. She recalled that she had experienced similar symptoms during a series of mersalyl injections six months previously. On the eighth hospital day she was given 2 cc. of Mercuhydrin at 9 a.m. and at 4 p.m. had a temperature of 103.5 F., chills, and severe muscular aching. This reaction was followed on the tenth, eleventh and twelfth days by injections of 2 cc. of Thiomerin, 96 mg. of theophylline sodium and 1.1 cc. of Mercuzanthin, respectively, none of which caused an untoward reaction. On the fourteenth day, the administration of 0.05 cc. of Mercuhydrin produced severe systemic symptoms and a fever of 103.2 F.

Case 3. A 50 year old white woman having rheumatic heart disease of functional class III with cardiac enlargement, aortic insufficiency, mitral stenosis and insufficiency, auricular flutter and mild congestive failure was hospitalized for treatment of the arrhythmia and decompensation. As represented in figure 4, she received Mercuhydrin intramuscularly at 9 a.m. daily for seven days prior to her first reaction on the sixth hospital day. The peak of the febrile response occurred at 4 p.m. and the reaction was characterized by a chill, diaphoresis, "drawing sensation" in the muscles and generalized malaise. Similar episodes followed the diuretic injections on the seventh and eighth hospital days. Mercuhydrin was discontinued on the ninth day. Fever-free days followed, during which she was given 96 mg. of theophylline sodium on the eleventh and 2 cc. of Thiomerin on the twelfth and thirteenth days. On the fourteenth day, she had a rather severe reaction following 0.05 cc. of Mercuhydrin but, on the following day, the injection of 2 cc. of Mercuzanthin caused no symptoms.

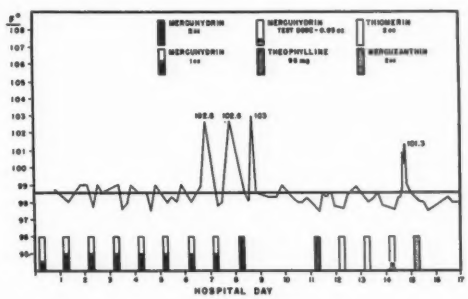

FIG. 4. Case 3. Temperature reactions

DISCUSSION

The fact that the reactions to Mercuhydrin occurred after a series of 6 to 11 apparently well tolerated injections suggested that they were due to hyponatremia or the development of hypersensitivity to the drug. Hyponatremia was not demonstrated in any case in which the serum sodium was determined. The development of typical reactions to minute amounts of the drug and the absence of any reaction to other mercurial diuretics support the hypothesis of specific hypersensitivity to the mercurial compound. The absence of reaction to theophylline sodium indicates that the hypersensitivity is to the mercurial component of the organic combination. The modification of the response to Mercuhydrin after the administration of Pyribenzamine, is further evidence of the allergic nature of the reactions.

British anti-lewisite has been reported to inhibit the diuretic effect of organic mercurial drugs,[17, 18, 19, 21] and to counteract the acute cardiac[19, 20, 23] and renal[22] toxicity of mercury in the laboratory. The administration of BAL also appears to prevent the development of typical hypersensitivity reactions to Mercuhydrin. The lack of reaction to Mercuhydrin on the day following administration of BAL in one case is difficult to explain.

Eventual disappearance of the allergic response was demonstrated in two patients. Hypersensitivity to Mercuhydrin was also observed by Gelfand[3] in a patient whose reactions were similar to those described and in whom a positive skin reaction was elicited with blood serum from another patient who was receiving and tolerating Mercuhydrin. The skin reaction became negative several months after the cessation of therapy.

The administration of mercurial diuretics forms an integral part of the effective management of cardiac decompensation, and there are few contraindications to their administration. Although thousands of injections of these drugs have been given without observed adverse effect, there exists a small number of patients who develop sensitivity after multiple well tolerated doses. During the period from March 1949 to January 1951 more than 16,000 cc. of Mercuhydrin were dispensed at the direction of the Cardiovascular Department of the Cleveland Clinic, and the reported cases represent the total evidence of intolerance so far as we are able to determine. It is important that one be cognizant of the manifestations of hypersensitivity to mercurial diuretics and regard even mild reactions as an indication for re-evaluation of therapy. Failure to appreciate the danger of continued administration may well result in fatalities. If there is need for further diuresis in a patient who has become hypersensitive to a given preparation, simply changing to another product appears to be a satisfactory solution.

Summary

The observations reported indicate that, in certain individuals, hypersensitivity to the mercurial component of Mercuhydrin is induced by a series of intramuscular injections of the drug. An investigation is in progress to ascertain whether or not the similar use of other mercurial diuretics will result in the development of analogous reactions.

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Paradoxic Action of Amyl Nitrite in Coronary Patients

By STEPHEN CONTRO, M.D., OLGA M. HARING, M.D., AND WALTER GOLDSTEIN

Amyl nitrite inhalation in patients with sclerotic coronary vessels is followed by electrocardiographic changes typical of temporary coronary insufficiency. It is suggested that, in such cases, a slight increase of cardiac work (tachycardia) together with a decrease of blood supply (fall in blood pressure), leads to myocardial ischemia. Comparison between an exercise test and amyl nitrite inhalation in the same patients indicates similar results. Amyl nitrite inhalation may be used as a simple functional test in borderline or questionable cases of coronary heart disease.

AMYL NITRITE was discovered by Balard[1] and further investigated by Guthrie[2] and Gamgee.[3] Brunton[4] observed that patients suffering from angina pectoris were promptly relieved by inhalation of the drug. In the following decades, the beneficial effects of several nitrous products were reported; some of them still represent the most used medication for angina pectoris. Nitrites, nitrous esters, and organic nitrates (which are reduced in the body to nitrites) cause a prompt drop of blood pressure. Their action is exerted directly on the smooth muscle of the arteries and is antagonistic to that of epinephrine.[5]

Angina pectoris is due to absolute or relative insufficiency of the coronary circulation, followed by myocardial anoxia. The nitrities act both on the coronary vessels, increasing the blood flow,[6, 7, 8] and on other arteries.[9] The peripheral effect consists of vasodilation followed by decreased work of the myocardium and decreased blood demand.

The beneficial effect of these drugs in most patients is an established fact. However, clinical experience has proved that, in certain patients, the use of nitrites is not followed by clinical improvement[4, 10, 11] and may even cause untoward effects.

Electrocardiographic changes after inhalation of amyl nitrite have been reported in the literature by various authors (Nagl,[12] Goepfert and co-workers,[13] Nordenfelt,[14] Langeron and associates,[15] Goldberger,[16] Ashman and Bayer,[17] and Scherf[18]). Goldberger attributes them to positional changes caused by deep inspiration; Nordenfelt compares them to those occurring in the change from the supine to the erect position.

The present study was prompted by the observation of paradoxic changes of the electrocardiogram suggesting ischemia of the myocardium after amyl nitrite inhalation.

MATERIAL AND METHOD

Fifty-nine adults of both sexes, ranging in age from 25 to 75 years, were studied. Ten were healthy young men and constituted a control group; 49 were ambulatory patients from the Cardiac Clinic of Mount Sinai Hospital and were divided into three groups. Group 1 included patients with angina pectoris and normal or borderline resting electrocardiogram; group 2 included patients with angina pectoris and an abnormal resting electrocardiogram; group 3 included patients with atypical anginal pain (four of them were patients with rheumatic heart disease with valvular deformities, three had no evidence of organic heart disease).

After a short period of rest in recumbent position, an electrocardiogram was recorded, using a direct writing Sanborn Poly-Viso. Standard leads, unipolar limb leads, and three chest leads (V_2, V_4, V_6) were recorded. At the same time, the blood pressure was taken. A brief explanation of the immediate subjective effects of amyl nitrite was given in order to avoid undue alarm of the patient. A pearl of 0.18 cc. of amyl nitrite (Lilly) was used in each test. A team of three took part in the study. One administered the drug, one took the blood pressure, the third recorded the tracings. An electrocardiogram was taken as soon as flushing of the face occurred. Unipolar limb leads and the three chest leads were recorded alternately until the tracing showed stabilization. Taking of the standard limb leads was omitted in subsequent tracings in

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order to save time, as they can be calculated from the unipolar limb leads. In several instances, changes of the tracing persisted after the blood pressure had returned to the previous level. The study was continued for about 10 minutes.

The following data were correlated: age and sex; clinical and electrocardiographic diagnosis; use of digitalis; systolic and diastolic blood pressures; heart rate; duration of the electrical systole (Q-T;) ratio of the electrical systole to electrical diastole (Q-T/T-Q ratio); S-T segment and T-wave changes; possible occurrence of premature ectopic beats. In evaluating the electrocardiographic changes, Master's criteria were employed.[19, 20]

The following data were accepted as evidence of abnormal response (ischemic reaction): displacement of the S-T segment of more than 1 mm. above or below the isoelectric line*; flattening or inversion of the T wave in any lead; premature ectopic beats, not present in the control tracing.

Twenty patients who had received amyl nitrite inhalation were also submitted to Master's "two-step test." Twelve of these had normal or borderline resting electrocardiogram (group 1), six had slightly abnormal electrocardiogram (group 2) and two others had a normal tracing and a history of atypical anginal pain (group 3). Patients with definite abnormalities of the resting electrocardiogram were not submitted to the Master test because of the danger represented by this procedure. The Master test was performed at least 24 hours after the inhalation of amyl nitrite and according to the original description of the author.[19]

Results

In 27 cases out of 59, the first electrocardiogram recorded after amyl nitrite administration showed definite changes from the control tracing. Within 10 minutes, the electrocardiograms of 17 cases reverted to the initial pattern while the changes further persisted in 10. The pattern of these changes corresponded to that usually seen in myocardial ischemia, consisting of displacement of the S-T segment, inversion of the T wave not associated with changes of the electrical position, or both (figs. 1 through 5). Fifteen of the 27 cases had clinical and electrocardiographic evidence of coronary heart disease (group 2). Nine of these cases presented alterations which persisted till the end of the experiment. Nine cases had a history of angina pectoris with a normal or borderline resting electrocardiogram (group 1). Two had rheumatic heart disease; one of them was receiving digitalis and had auricular fibrillation, while the other had a normal tracing at rest (group 3). One case belonged to the supposedly normal control group. In two instances (group 2), appearance of ventricular premature beats was noted beside the S-T and T changes. Case 7 of group 1 did not show S-T or T changes. However, it was classified among those with an abnormal response because of the onset of nodal premature beats with aberrant con-

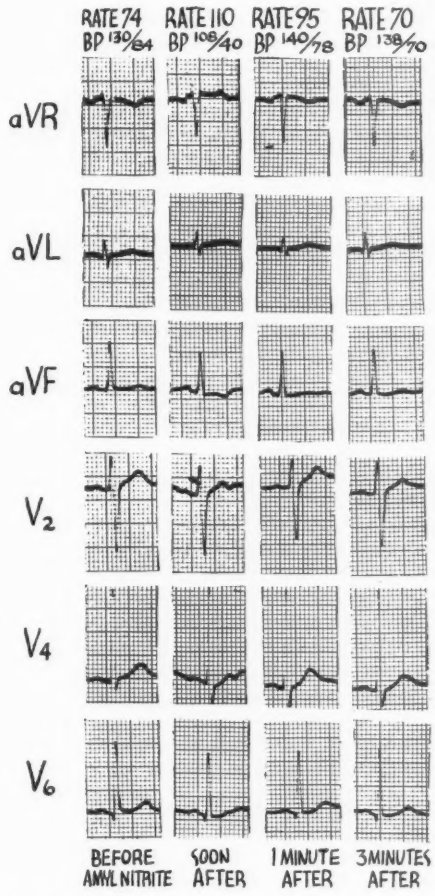

Fig. 1. Paradoxic action of amyl nitrite in a 28 year old normal subject.

* The P-Q level was considered as the isoelectric line because it does not change with an increased heart rate. In severe tachycardia, the T-P segment may not represent the isoelectric line because atrial depolarization may start before cessation of the ventricular repolarization.[21]

duction and abnormal prolongation of electrical systole.

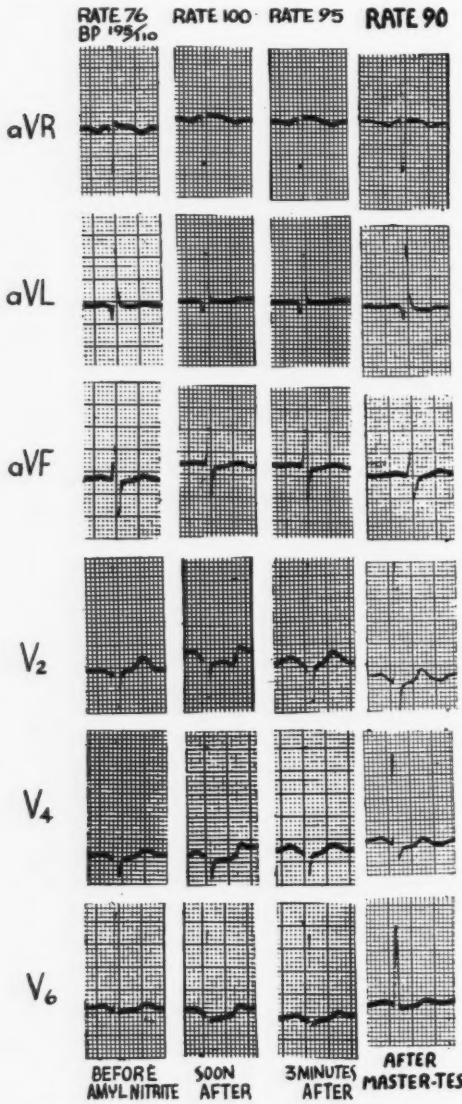

FIG. 2. Paradoxic action of amyl nitrite in a 52 year old hypertensive patient with angina pectoris. Control electrocardiogram and effect of amyl nitrite inhalation. Result of Master's test on a different day.

Blood pressures dropped in all cases during inhalation of the drug and usually returned to the control level within one minute. In several cases, however, blood pressure rose above control level before stabilizing. The drops of mean systolic and diastolic pressures were calculated in each case. An increase of the heart rate following the drop of blood pressure was noted in all cases but two. In the great majority

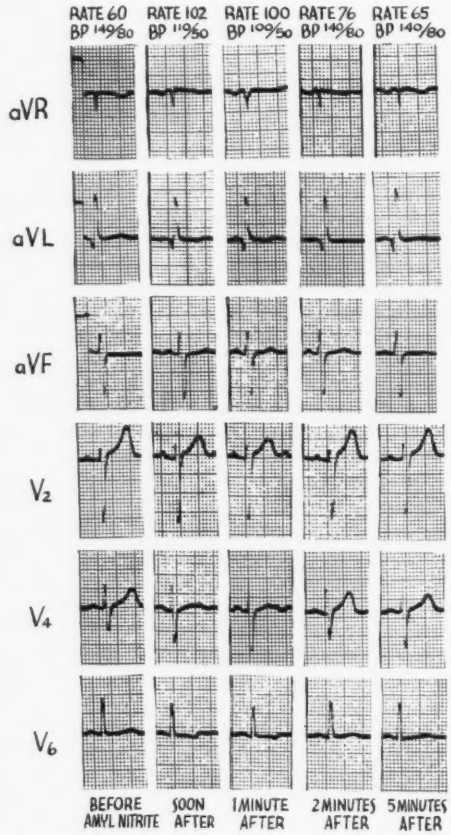

FIG. 3. Paradoxic action of amyl nitrite in a 65 year old arteriosclerotic patient. Control and various tracings after amyl nitrite.

of cases (40 out of 59), the rate was still slightly elevated after 10 minutes.

Among the 20 patients in whom both Master's and the amyl nitrite test were performed, six showed a positive and eight a negative response to both procedures; one presented a positive response to the Master test only, and another a positive response to amyl nitrite inhalation only. The results in the various groups are presented in table 2.

Discussion

Our study revealed that in 27 out of 59 subjects (45 per cent), amyl nitrite inhalation was followed by electrocardiographic changes similar to those usually seen in myocardial

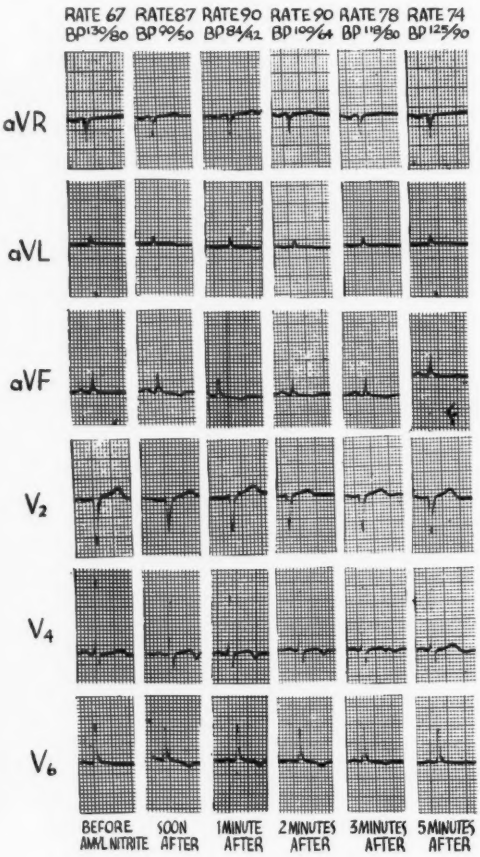

Fig. 4. Paradoxic action of amyl nitrite in a 57 year old coronary patient with angina pectoris. Control and various tracings after amyl nitrite.

ischemia. A possible relationship of these changes with either the modification of the heart rate or that of the blood pressure was considered.

Heart Rate. In several instances, the tracing showed electrocardiographic modifications when the heart rate increased and these changes disappeared with the return of the heart rate to previous values (four cases in group 2; one among the controls; one in group 3) (fig. 1). This would suggest a connection between electrocardiographic modifications and tachycardia.[22] However, the electrocardiographic changes were observed even when the cardiac rate increased but slightly (one case in group 1). In other cases, no abnormal response was observed when the rate became very rapid (seven cases in the control group; one in group 1), or the electrocardiographic changes were still present when the rate had returned to normal or had fallen below the control values (two cases of group 2).*

Blood Pressures. A slightly greater mean fall in blood pressure was presented by subjects showing the "ischemic" type of reaction in comparison with the others (table 1). The highest percentage of "ischemic" changes (60 per cent) occurred in patients having a history of angina pectoris but no definite electrocardiographic evidence of coronary heart disease. The changes were more permanent among cases having an abnormal electrocardiogram before the test (55.5 per cent).

In the patients subjected to both the Master test and amyl nitrite inhalation, the results of the two procedures were similar with the exception of two cases. In the first, amyl nitrite caused an "ischemic" reaction while Master's test did not modify the tracing. In the second, the opposite was true. However, while performing the Master test the patient experienced an attack of angina pectoris; amyl nitrite was immediately administered and was followed by increased severity of the electrocardiographic changes (fig. 5).

Coronary insufficiency is caused by a disproportion between blood supply and blood demand. The use of amyl nitrite, as well as that of other powerful vasodilators, is open to question. The increase of coronary flow may not be equivalent to the increased work (or

* Nordenfelt observed electrocardiographic changes after amyl nitrite in a case of complete A-V block. This further indicates the lack of connection between electrocardiographic changes and modifications of the ventricular rate.

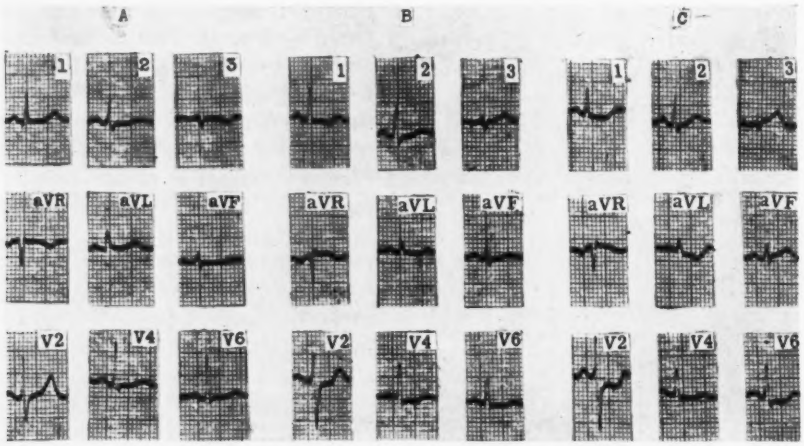

FIG. 5. Fifty-nine year old patient with hypertension and angina pectoris. (*A*) Control. (*B*) After Master's test (anginal pain). (*C*) After inhalation of amyl nitrite immediately following Master's test.

TABLE 1.—*Results Following Amyl Nitrite Test*

	Controls		Group 1		Group 2		Group 3	
Clinical Diagnosis	No evidence of cardiac disease		Angina pectoris		Coronary heart disease		Atypical angina pectoris	
Resting ECG	Normal		Normal or borderline		Abnormal		Either normal or abnormal	
Total cases	10		15		27		7	
	Paradoxical	No reaction	Paradoxical	No reaction	Paradoxical	No reaction	Paradoxical	No reaction
Reaction to amyl nitrite	1(10%)	9(90%)	9(60%)	6(40%)	15(55.5%)	12(44.5%)	2(28.3%)	5(81.7%)
Mean BP drop in mm. Hg	22/44	25/24	40/16	34/5	48/17	29/11	25/20	19/5
Mean heart rate increase (per minute)	36	36	32	17	24	12	24	28
Average cycle	28.00	28.00	59.42	65.33	61.46	65.50	46.66	46.00

TABLE 2.—*Comparison of Results Following the Master Test and Amyl Nitrite Inhalation*

	Group 1		Group 2		Group 3	
Clinical Diagnosis	Angina pectoris		Coronary heart disease		Atypical angina pectoris	
Resting ECG	Normal or Borderline		Abnormal		Either normal or abnormal	
Total cases	12		6		2	
	Positive	Negative	Positive	Negative	Positive	Negative
Reaction To:						
Master's test	6	6	6	0	0	2
Amyl nitrite	6	6	6	0	0	2
Positive To Only:						
Master's test	1		0		0	
Amyl nitrite	1		0		0	

the increased oxygen consumption) of the heart. Moreover, coronary dilatation may be counteracted by a sudden and dramatic drop of the aortic pressure to the point at which coronary flow may actually decrease. It is true that the low blood pressure is followed by decreased cardiac work if the rate of the heart fails to increase beyond certain limits. However, the reduction of the coronary flow caused by low aortic pressure may be greater than the reduction of work.

Our observations suggest that, if the coronary arteries are sclerotic and narrowed, a slight increase of cardiac work (increase of rate) together with a decrease of blood supply (fall in blood pressure) may lead to coronary insufficiency. Therefore, vasodilators should not be given in too large a dose or too rapidly, whenever coronary pathology is suspected.

It is suggested that amyl nitrite inhalation represents a new and simple test for borderline or questionable cases of coronary heart disease.

Summary

Electrocardiographic studies were made in 49 cardiac patients and 10 control subjects after inhalation of amyl nitrite.

In 27 cases out of 59, the first tracing recorded after amyl nitrite inhalation showed a pattern of ischemia; for example, displacement of S-T and flattening or inversion of T in one or more leads. Fifteen of these cases had clinical and electrocardiographic evidence of coronary heart disease, while nine had only a history of angina pectoris. Only one case of the control group showed similar changes.

While the increase of cardiac rate did not seem related to the observed changes, the drop in blood pressure was always definitely connected with them.

In 20 cases, comparison was made between the results of the Master test and those of amyl nitrite inhalation. These results were similar in 18 of them.

It is suggested that, whenever the coronary arteries are sclerotic, the sudden blood pressure drop caused by amyl nitrite may be followed by coronary insufficiency.

Amyl nitrite inhalation may be used as a functional test in borderline or questionable cases of coronary heart disease.

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Acceleration of Blood Coagulation in Acute Myocardial Infarction as Demonstrated by the Heparin Clotting Time; Effect of Dicumarol Therapy

By Robert L. Rosenthal, M.D. and John C. Weaver, M.D. with the technical assistance of Agnes Benedek, B.S.

A study of blood coagulation was made on cardiac patients with and without acute myocardial infarction, prior to anticoagulant therapy. The heparin clotting time, an in vitro modification of the heparin tolerance test, was accelerated in 74 per cent (14 out of 19) of the patients with acute myocardial infarction studied within three weeks after the attack. One out of 14 patients without acute myocardial infarction had an accelerated heparin clotting time below 20 minutes, the lower limit of the "normal" range established on the basis of study of over 100 control subjects. The clotting time and platelet count revealed no significant variations. Serial coagulation studies, performed on patients receiving Dicumarol therapy, revealed that the heparin clotting time, which provides a sensitive measure of over-all coagulability, is prolonged as the prothrombin concentration is diminished. The significance of these findings in relation to thromboembolic complications of acute myocardial infarction and anticoagulant therapy is discussed.

INVESTIGATION OF the basic abnormalities of the clotting mechanism in thrombo-embolic diseases has been summarized in the Transactions of the Conference on Blood Clotting of the Josiah Macy Jr. Foundation 1947–1951 but there are many aspects of this complicated field which are left unanswered. This is particularly true for acute myocardial infarction where the primary insult of occlusion of a coronary vessel and many secondary complications are largely attributable to thrombo-embolic phenomena, which may be effectively diminished by anticoagulant therapy.[1] Emphasis on research related to clotting in myocardial infarction has accordingly been placed upon the development and control of anticoagulant drugs.

The most effective method for the detection of accelerated clotting evolved from the heparin tolerance principle developed by De Takats[2] and Waugh and Ruddick.[3] These workers measured the effect of added heparin in prolonging the clotting time and found that patients with thrombo-embolic disease tended to clot faster than "normal" control subjects. Numerous modifications of this test have since been reported, but the results have been variable. This can be attributed in part to the complex and time-consuming nature of these technics, which have frequently been inadequately standardized and hence are difficult to interpret. A simplified test using the heparin tolerance principle has been developed in this laboratory. This test, called the heparin clotting time, has given consistent results and has been standardized on a large series of control subjects to give well-defined upper and lower limits of normal.[4] The use of this test in the study of a group of patients with acute myocardial infarction, and the effect of Dicumarol therapy are here reported.

From Donner Laboratory, Division of Medical Physics and the Radiation Laboratory, University of California, Berkeley, and the Highland-Alameda County Hospital, Oakland, Calif. This study was supported in part by the Donner Foundation.

Methods and Procedure

Two groups of patients were chosen for study: (1) Nineteen patients with the clinical picture of acute myocardial infarction corroborated by electrocardiogram. (2) Fourteen patients with cardiovascular disease as specified in table 1 but without evidence of acute myocardial infarction. Studies were performed on all patients prior to therapy with anti-

TABLE 1.—*Data in 14 Patients with Cardiovascular Disease and without Acute Myocardial Infarction*

Patient	Age	Sex	Diagnosis*	Day of hospital stay studied	Clotting time	Heparin clotting time	Platelet count	Hematocrit
					min.	*min.*	*per cu. mm.*	%
H.K.†	55	F	ASHD Failure	14	8	13	380,000	42
V.C.	74	F	ASHD	5	8	21	540,000	43
R.W.	68	F	ASHD	9	9	21	290,000	41
C.G.	69	M	ASHD	4	6	23	340,000	38
N.B.	75	F	ASHD	6	6	25	300,000	41
E.F.	69	M	ASHD	23	8	25	360,000	31
M.G.	66	F	ASHD Failure	3	14	28	190,000	43
E.C.	88	M	ASHD	2	6	28	370,000	33
A.S.	73	F	H & ASHD Failure	5	6	28	410,000	42
E.S.	70	F	RHD, inactive	3	7	29	240,000	30
E.N.	79	F	ASHD Failure	9	6	35	330,000	42
J.C.	57	M	H & ASHD Diabetes	2	11	39	470,000	31
J.S.	82	F	ASHD	8	15	42	270,000	33
F.L.	85	M	ASHD	3	12	53	260,000	41

* ASHD refers to arteriosclerotic heart disease; H refers to hypertensive heart disease; RHD refers to rheumatic heart disease.

† Died 3 days after test; cause of death not known.

TABLE 2.—*Data in 19 patients with Acute Myocardial Infarction*

Patient	Age	Sex	Day of hospital stay studied	Clotting time	Heparin clotting time	Platelet count	Hematocrit
				min.	*min.*	*per cu. mm.*	%
E.A.	66	F	7	6	12	550,000	39
J.G.	72	F	7	6.5	11	210,000	38
J.R.*	76	M	6	7	13	400,000	41
M.G.	65	M	2	8	14	270,000	42
F.C.	69	F	4	6	15	370,000	39
S.E.	62	F	3	6	15	250,000	42
M.C.	74	F	4	5	16	450,000	42
C.S.	72	F	10	6	16	500,000	40
A.L.	84	F	6	5	16	430,000	43
M.K.	68	F	2	7	17	340,000	44
M.L.	58	M	10	6	17	270,000	38
W.B.	59	M	7	6.5	18	425,000	37
H.G.	59	M	3	7	18	260,000	43
H.E.	39	M	2	6	19	330,000	54
O.R.	43	M	3	5.5	20	340,000	43
J.A.	70	M	2	6	21	375,000	36
L.J.	60	M	1	7.5	25	430,000	43
E.S.	75	M	3	8	26	260,000	39
E.R.	54	F	12	16	47	190,000	61

*Patient in cardiac failure.

coagulants, usually during the first week of hospitalization as indicated in tables 1 and 2. Serial studies were performed on a group of patients during Dicumarol therapy for acute myocardial infarction.

Blood was drawn with a dry syringe and a 20 gage needle. Care was exercised to avoid trauma in order to minimize contamination with tissue juice. The first and last cubic centimeter of blood in the syringe were discarded. The following tests were done: clotting time, heparin clotting time, platelet count and hematocrit. The clotting time and heparin clotting time were done according to methods described in a previous report.[4] In essence, both tests were performed in a water bath set at 37 C., and the end point of clotting was timed from the appearance of the blood in the syringe to the formation of a firm clot upon inversion of the test tube. For the clotting time, 1 cc. of blood was placed in a glass tube 13 mm. by 100 mm. in size. A similar procedure was used for the heparin clotting time in which the 1 cc. of blood is added to and mixed with 4 μg. of heparin* dissolved in 0.1 cc. of 0.85 per cent saline. The platelet count was performed in the counting chamber, using Rees-Eckers fluid as the diluent. Hematocrits were performed on heparinized blood in a Wintrobe tube. Prothrombin times were performed upon whole plasma of the patients receiving Dicumarol and the result was expressed in per cent prothrombin concentration, according to the one-stage method described by Quick.[5]

* The various commercial preparations of heparin in aqueous solution have been found to give comparable results in this test.

Results

The results are tabulated in tables 1 and 2 for patients without and with myocardial infarction, respectively. Table 3 presents a summary of the results. The outstanding finding is a significantly rapid heparin clotting time of less than 20 minutes in 14 subjects or 74 per cent of the patients with acute myocardial infarction, while only one patient in the group with cardiovascular disease without myocardial infarction had a rapid heparin clotting time. The definition of the normal range of the heparin clotting time between 20 and 35 minutes with an average value of 27 minutes has been based on previous determinations in over 100 control subjects, ranging in age from the second to seventh decade. The clotting times, platelet counts and hematocrit values showed slight but not significant differences between the two groups of patients. The presence of cardiac failure in a few of the subjects appeared to have no effect upon the tests performed.

Table 3.—*Summary of Results in Patients with and without Acute Myocardial Infarction*

	Patients with acute myocardial infarction	Patients without acute myocardial infarction
Number of patients	19	14
Average age (yrs.)	64	72
Clotting time, mean value (min.)	6.9	8.7
Heparin clotting time, mean value (min.)	18.7	29.3
Less than 20 min., number & % of pts.	14—74%	1—7%
20 to 35 min. (normal or control range)	4—21%	10—71%
Above 35 min.	1—5%	3—22%
Platelet count, mean value (per cu. mm. of blood)	350,000	340,000
150,000 to 400,000 (normal range), number & % of pts.	12—62%	11—78%
Above 400,000	7—38%	3—22%
Hematocrit, mean value, %	42	38

Serial coagulation studies during Dicumarol therapy are shown in figure 1. As the prothrombin concentration decreased after Dicumarol, the heparin clotting time became prolonged to levels of about 28 to 35 minutes as compared with pretreatment values of 15 to 25 minutes. In a few instances, the heparin clotting time reached 50 to 60 minutes without any marked change in the prothrombin concentration which remained about 15 per cent. The data for one patient who developed a heparin clotting time above 120 minutes with a 26 per cent prothrombin concentration is presented in table 4. The clotting time was occasionally prolonged and the platelet count showed no significant changes during Dicumarol therapy.

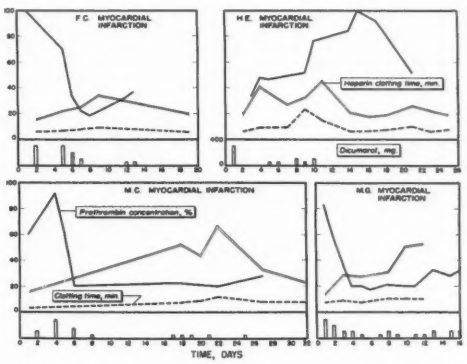

Fig. 1. Plots of Dicumarol dosage, prothrombin concentration, clotting time and heparin clotting time in four patients receiving Dicumarol therapy for acute myocardial infarction.

Table 4.—*Serial Clotting Studies During Dicumarol Therapy in a Patient with Acute Myocardial Infarction (J.W.)*

Date	Dosage of Dicumarol	Prothrombin concentration	Clotting time	Heparin clotting time	Platelet count
		%	*min.*	*min.*	*per cu. mm.*
9/14/49	9/10/49	16	9	29	450,000
9/16/49	to	33	10	31	390,000
9/19/49	9/29/49	31	7.5	21	340,000
9/21/49	1500	44	8	22	360,000
9/23/49	mg.	48	9	25	310,000
9/26/49	total	46	7	27	250,000
9/28/49		28	8.5	26	260,000
9/30/49		26	22	120	340,000
10/3/49		42	9	45	350,000
10/5/49		—	21	57	380,000
10/10/49		100	7	28	280,000

Discussion

In this study, accelerated coagulability was demonstrated by the heparin clotting time in 74 per cent of patients with acute myocardial infarction. This finding is in agreement with the results of Ogura and co-workers.[6] who found an increased coagulability in 77.8 per cent of 27 patients with acute myocardial infarction, using the Waugh and Ruddick heparin retarded clotting test. These authors found the accelerated clotting to be most marked between the second and seventeenth days after the onset of infarction and felt that the accelerated coagulability followed the attack rather than preceded it. On the other hand, Hilton and associates[7] were unable to detect any significant alterations in the Waugh and Ruddick test in acute myocardial infarction. Several authors have demonstrated a shortening of the dilute prothrombin time in patients with acute myocardial infarction.[8–10]

The mechanism of the increased coagulability as demonstrated by a decreased sensitivity to the anticoagulant effect of heparin is not known. Experiments on the heparin clotting time in a wide variety of experimental and clinical conditions have shown that the test reflects the over-all state of coagulability of the blood.[11] The deficiency of one or more known factors in the clotting mechanism, such as platelets, prothrombin, plasma and serum Ac-globulin and antihemophilic globulin, has been found to render the blood more sensitive to the anticoagulant action of heparin and to give a prolonged heparin clotting time. On the other hand, an excess of one or more clotting factors, such as platelets or thromboplastin, make the blood more resistant to the anticoagulant effect of heparin, and will result in an abnormally rapid heparin clotting time. In the present study, no increase in platelet count occurred in conjunction with the accelerated clotting. However, this does not exclude the possibility of qualitative changes in platelets, such as in adhesive and agglutination properties, as factors in the increased coagulability. The amount of thromboplastin and its precursors in the blood is probably of great importance in all thromboembolic diseases, but the exact nature of thromboplastin is obscure and subject to controversy. Deficiency of normal circulating clotting inhibitors such as antithrombin or endogenous heparin derived from the mast cells may account for the rapid coagulability. Whatever its significance and mechanism, it appears that the increased coagulability of the blood in acute myocardial infarction portends a threat of thrombo-embolization and is further indication of the importance of anticoagulant therapy to decrease the clotting tendency.

This study indicates that the heparin clotting time is markedly altered following Dicumarol therapy. As the prothrombin concentration decreases, the heparin clotting time increases. Recent reports have emphasized the need for accurate and frequent checks of the prothrombin time in order to avoid hemorrhagic complications during Dicumarol therapy.[12, 13] With good prothrombin time control during Dicumarol therapy, however, bleeding is sometimes seen in the presence of relatively high prothrombin concentrations, as shown recently by Hogben and Allen.[14] Recently, two patients on Dicumarol therapy developed bleeding manifested by epistaxis and hematuria with prothrombin times in the range of 16 to 19 seconds (control 12 seconds). In each case, the heparin clotting time was prolonged to about 60 minutes.[15] This situation may be partly attributed to the presence of slight pre-existing clotting deficiencies which lead to hemorrhage after minor drops in prothrombin concentration. Since the prothrombin time measures only part of the clotting mechanism because of the use of an excessive amount of thromboplastin in its determination, abnormalities in the "thromboplastic elements" would remain undetected. This situation also prevails in thrombocytopenias of various etiologies and in hemophilia. Because the heparin clotting time provides a sensitive measure of over-all coagulability, it would reveal any clotting deficiency before therapy and may be of value in establishing therapeutic levels and in minimizing the risk of hemorrhage during anticoagulant therapy. Further study and evaluation of anti-

coagulant therapy controlled with the aid of the heparin clotting time is now in progress.

Summary

A study of blood coagulation before anticoagulant therapy in a group of 19 patients with acute myocardial infarction revealed accelerated coagulability in 14 or 74 per cent of the patients as detected by the heparin clotting time. Only one or 7 per cent of 14 patients with cardiovascular disease but without acute myocardial infarction simultaneously studied had a rapid heparin clotting time. The clotting times and platelet counts were normal in both groups of patients.

The significance of this hypercoagulability in acute myocardial infarction in relation to thrombo-embolic complications and additional rationale in favor of anticoagulant therapy is discussed.

Dicumarol therapy was found to have a marked effect in prolonging the heparin clotting time which provides a sensitive measure of over-all coagulability and, hence, may be a valuable test in the control of anticoagulant therapy. Whether the heparin clotting time follows the prothrombin activity or other clotting indexes closely enough to be the *sole* guide for therapy with the coumarin derivatives and phenylindandione must await further investigation and experience.

Acknowledgements

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Further Studies on the Effect of Arteriovenous Fistulas and Elevations of Sinus Pressure on Mortality Rates Following Acute Coronary Occlusions

By GEORGE SMITH, F.R.C.S., JAMES DEMMING, MORTON ELEFF, AND RICHARD W. ECKSTEIN, M.D.

Observations were made on the mortality rates within the first hour following acute ligation of the circumflex artery. The experiments were divided into the following groups: (1) those with arteriovenous fistulas, (2) those with elevation of coronary sinus pressure, (3) those with complete coronary sinus occlusion, and (4) those with arterialization of the coronary sinus. There was a mortality of 70 per cent in the first group, 30 per cent in the second group, 40 per cent in the third group, and no deaths in the fourth group. The results indicate that arterialization of the coronary sinus provides the greatest protection against ventricular fibrillation and that such arterialization provides the only practical means of chronically elevating coronary sinus pressures to effective levels.

PREVIOUS investigations[1] have shown that acute arterialization of the coronary sinus in dogs leads to remarkable protection against acute ventricular fibrillation during the first hour following acute coronary artery ligation. Although no attempts were made to analyze the exact mechanism of the protective nature of this procedure certain questions were raised at that time. It is the purpose of this report to repeat some of our previous experiments and to present the results of studies to determine whether there are beneficial effects from: (1) arteriovenous fistulas as close as possible to the heart, (2) simple elevation of coronary sinus pressure without arterialization of the sinus, and finally (3) complete coronary sinus occlusion without arterialization of the sinus. This study deals with comparisons of acute mortality rates within one hour in dogs following circumflex artery ligation with each of the above named variables. It is hoped that through these studies facts may be obtained which will lead to an understanding of the exact physiologic processes operating to protect the heart after the coronary sinus anastomosis of Beck and his associates.[2–5]

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METHODS AND RESULTS

Mongrel dogs varying in weight from 8 to 21.5 Kg. were anesthetized with morphine and pentobarbital. Under artificial respiration the left chest was opened between the fourth and fifth ribs. The pericardium was slit and the circumflex artery was dissected free at its origin and a loose ligature was placed beneath it. The left subclavian artery was treated likewise. The coronary sinus was isolated. The animal was heparinized and a long, glass cannula was passed to the level of the right auricle through the left jugular vein. A cannula was also placed in the aorta by way of the left common carotid artery for optical recordings of blood pressure. Electrocardiograms were taken and usually lead aV_R was used. At this point the procedure was varied so as to divide the experiments into four groups.

Group 1. Arteriovenous Fistulas

This group consisted of 10 dogs whose average weight was 12.7 Kg. An arteriovenous fistula was created by an appropriate connection between the left subclavian artery and the right auricle through the left jugular

cannula. In an effort to handle these hearts exactly as in the other groups a cannula was passed through the tip of the right auricle into the coronary sinus where it was secured with a ligature. The sinus blood entered the right auricle through a wide side opening in the cannula. The external end of the cannula remained closed. After the electrocardiograms and optical aortic pressures were recorded the arteriovenous fistula was opened. Its magnitude was estimated by measuring the fistula flow into a graduate held at the level of the jugular vein. A further set of records were taken.

QRS complex, with a deep inversion of the T wave and a marked depression of the S-T segment. These changes occurred in all dogs whether they died with ventricular fibrillation or survived for one hour. The blood flow through the fistulas ranged from 240 cc. per minute to 420 cc. per minute with an average of 344 cc. per minute. (See table 1.)

Group 2. Elevation of Coronary Sinus Pressure

This group also consisted of 10 dogs whose average weight was 12.6 Kg. The coronary sinus was cannulated through the tip of the

TABLE 1.—*Average Data for Each Group*

	Group 1	Group 2	Group 3		Group 4
	A.V. Fistulas	Sinus Pressure Elevation	A—Arterialization	B—Sinus Pressure Elevation	Coronary Sinus Occlusion
Dog weights (Kg.)	12.7	12.6	13.9	13.7	14.1
Percentage of total heart weight made ischemic by circumflex ligation	37	43	42	44	40
Mean aortic pressure prior to opening of A.V. fistulas, elevation of sinus pressure, arterialization of sinus or sinus occlusion (mm. Hg)	79	88	103	112	111
Mean aortic pressure after manipulation as above but prior to circumflex ligation (mm. Hg)	75	87	89	109	100
Mean aortic pressure one hour after circumflex ligation (mm. Hg) (surviving dogs)	79	75	69	84	70
Mean coronary sinus pressure prior to circumflex ligation (mm. Hg)		40	45	39	48
Mean coronary sinus pressure 30 seconds after circumflex ligation (mm. Hg)		37	43	35	38
Survival time (all dogs) (minutes)	27	50	60	50	50
Survival time for dogs dying in less than one hour (minutes)	13	39		28	39
Per cent surviving for one hour	30	60	100	80	60

After changes ceased to occur the circumflex artery was ligated at its origin and the animal was observed for one hour. At the close of the experiment the ischemic area was injected with India ink, cut out and weighed. This was done also in all the experiments described below.

In this group of 10 dogs with arteriovenous fistula three dogs survived for one hour following circumflex ligation. Seven dogs died in from $1\frac{1}{2}$ to 58 minutes, with an average survival time of 13 minutes. All dogs showed the usual rapid cardiographic changes in aV_R consisting of an increased amplitude of the

right auricle. The cannula was made secure with a ligature and the sinus pressure was optically recorded. The sinus blood was led into the left jugular vein. The left subclavian artery was ligated. In an effort to maintain a high mean sinus pressure of about 50 mm. Hg and to reduce the high levels of sinus systolic pressure, an air chamber was placed in the tubing between the sinus and the jugular vein (fig. 1). After control records were obtained a clamp was placed near the jugular cannula distal to the air chamber to elevate sinus pressure. To produce mean pressures of 50

mm. Hg to compare with previous sinus arterialization experiments[1] it was often necessary to completely occlude the sinus outflow. After records were obtained and a steady state was reached, the circumflex artery was ligated as before and the animal was observed.

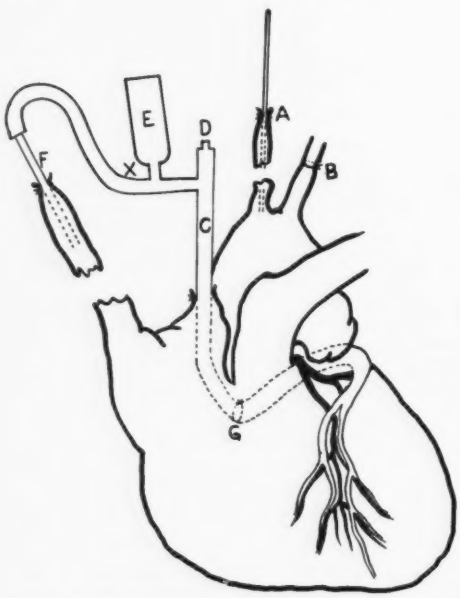

FIG. 1. Showing experimental method for simple elevation of coronary sinus pressure. (A) Cannula through left common carotid artery to aorta for aortic pressure; (B) ligature about left subclavian artery; (C) coronary sinus cannula introduced through right auricle; (D) outlet to record coronary sinus pressure; (E) air chamber of 25 cc. capacity; (F) cannula through left external jugular vein to level of right auricle; (G) ligature about tip of cannula in coronary sinus; (X) point of constriction for elevation of sinus pressure.

There were 10 dogs in this group whose mean coronary sinus pressure averaged 40 mm. Hg at the time of circumflex ligation. There was an average drop of 3 mm. Hg in mean sinus pressure 30 seconds after circumflex ligation. In this series, six dogs survived for one hour and four died in ventricular fibrillation in an average time of 39 minutes. The average mean aortic pressure in the six surviving dogs was 75 mm. Hg one hour after circumflex ligation. Electrocardiographic changes were as described above (table 1, group 2).

Group 3. Arterialization of the Coronary Sinus Alternating with Elevation of Sinus Pressure

In this group there were 20 dogs which were divided into two groups of 10 each.

A. Arterialization of the Coronary Sinus. This group of 10 dogs had an average weight of 13.9 Kg. The sinus was cannulated with the cannula described previously.[1] After the control records were obtained the sinus was arterialized at a mean pressure of 50 mm. Hg and the circumflex ligated. Arterialization of the sinus produced a fall in average mean aortic pressure from 103 to 89 mm. Hg. The average mean coronary sinus pressure before circumflex ligation was 45 mm. Hg, and immediately after artery ligation the average mean sinus pressure was 43 mm. Hg. One hour after circumflex artery ligation there were 100 per cent surviving dogs whose average mean aortic pressure was 69 mm. Hg. Previously described electrocardiographic changes were present[1] (table 1).

B. Elevation of Sinus Pressure. Alternating with the 10 dogs in *A* were the 10 dogs in this group whose weights averaged 13.7 Kg. These dogs were prepared and handled exactly as in group 2 above with simple elevation of sinus pressure. This was done so as to study more adequately the effects of sinus pressure elevation and to control the possible variations in technic.

The average initial mean aortic pressure was 112 mm. Hg. This pressure fell to an average of 109 mm. Hg when the mean pressure in the sinus was raised to an average of 39 mm. Hg. The sinus pressure fell an average of 4 mm. Hg when the circumflex artery was ligated. At the end of one hour there were eight surviving dogs whose mean aortic pressure was 84 mm. Hg. The two deaths occurred in an average of 28 minutes (table 1, group 3B).

Group 4. Complete Sinus Occlusion

The 10 dogs in this group had an average weight of 14.1 Kg. The coronary sinus was cannulated with a rigid cannula with connections

for optically recording sinus pressure and for diverting the sinus blood into the jugular cannula prior to sinus occlusion. After control records were obtained closure of a stopcock served completely to occlude the sinus. When stable conditions were reached the circumflex artery was ligated and the fate of the animal was awaited.

These 10 dogs had an initial mean aortic pressure of 111 mm. Hg which fell to 100 mm. Hg when the sinus was completely occluded. Such sinus occlusion resulted in a mean coronary sinus pressure of 48 mm. Hg. Circumflex artery ligation resulted in an average decline in the mean sinus pressure of 10 mm. Hg. Six of these dogs lived one hour at which time the average mean aortic pressure was 70 mm. Hg. Death occurred in the remaining four dogs in an average of 39 minutes (table 1). The electrocardiographic changes following circumflex ligation were as described above.

Discussion

It was previously found that, in our hands, ligation of the circumflex artery at its origin is attended by a mortality of 70 per cent within one hour.[1] In these present studies the presence of an arteriovenous fistula which emptied into the right auricle did not modify the mortality resulting from circumflex artery ligation. Therefore, we believe that the arteriovenous fistula itself is of no significance in providing the remarkable protection to the heart which results from arterialization of the coronary sinus.

The 10 dogs reported here which survived circumflex ligation after arterialization of the sinus together with the 10 previously reported[1] give considerable support to the view that this procedure is protective against ventricular fibrillation. The questions naturally arise whether the benefits from this procedure are due to arterialization of the sinus and whether identical benefits can be expected by simple elevation of sinus pressure.

The 70 per cent survival rate in 20 experiments described here with simple elevation of sinus pressure gives substantial proof that this procedure is also decidedly protective. It must be pointed out, however, that in many dogs a mean sinus pressure of 50 mm. Hg is impossible to attain by simple restriction of sinus outflow. It is believed that the anatomic arrangement of veins may explain the low sinus pressure in certain dogs. Usually a large posterior vein drains into the ostium of the coronary sinus and therefore it does not share in the elevation of venous pressure. Since there are frequently large communications at the cardiac apex between branches of anterior veins and this posterior vein there exists a large low-pressure drainage channel which may make the maintenance of high sinus pressure impossible.

Likewise the studies of Thornton and Gregg[6] revealed the impossibility of chronic marked elevation of coronary sinus pressure by simple sinus ligation since in their experiments even after one month of chronic sinus ligation the acute high pressure had been replaced by pressures only slightly higher than control pressures. It is noteworthy, however, that in a small series all of their dogs survived combined arterial and venous ligation. Gross[7] was likewise able to reduce his mortality rates by partial elevation of coronary sinus pressure induced by partial occlusion. Our own studies showing 30 per cent mortality with sinus pressure elevation and 40 per cent mortality with complete sinus occlusion are not significantly different from each other. However, when compared with the 20 dogs with sinus arterialization reported here and elsewhere[1] there is a significant difference, since the p values are .02 for the group with sinus pressure elevation and .015 for the group with complete sinus occlusion.

By means of the expansion chamber it was hoped to approximate the mean sinus pressures induced by arterialization and to prevent the attainment of deleterious high systolic pressures. However, an inspection of table 1 reveals that exact duplication of mean sinus pressures was not obtained. Therefore, one cannot, from these experiments, separate the effects of arterialization from those of pressure elevation. The fact remains though, that only by arterialization can suitable chronic elevations in sinus pressure be realized.

It is believed that these studies offer con-

vincing proof that arterialization of the coronary sinus at a mean pressure of about 50 mm. Hg offers the greatest degree of protection against ventricular fibrillation when compared with other methods of raising the sinus pressure. The attainment and maintenance of effective pressures by other means would require the use of pumps and therefore is impractical.

Although much speculation is possible, the true factors which provide protection for the heart are unknown. Physiologic studies have been begun to test whether this procedure creates pressure relationships likely to supply blood to ischemic capillaries from the arterialized sinus during the critical period following occlusion of a coronary artery, or establishes conditions which enable existing but nonfunctioning collaterals to become functional. Although the value of arterialization of the coronary sinus following acute coronary occlusion in dogs is unquestionable, it is the conviction of the authors that these studies neither confirm nor deny the question of the effectiveness of this procedure in the treatment of human angina pectoris.

Summary

Mortality rates due to acute ligation of the circumflex artery have been determined. Comparisons are made of the value of various procedures in protecting the heart against ventricular fibrillation. It has been found that there is a mortality of 70 per cent within one hour following artery ligation in the presence of an arteriovenous fistula. This mortality is reduced to 30 per cent when coronary sinus pressure is elevated and to 40 per cent when the sinus is completely occluded. There were no deaths from circumflex artery ligation in the presence of sinus arterialization. It is concluded that arterialization of the sinus provides not only superior protection but is also the only practical means for chronic maintenance of effective sinus pressure.

Acknowledgment

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Further Observations on Penicillin-Treated Cardiovascular Syphilis

By JOSEPH EDEIKEN, M.D., WILLIAM T. FORD, M.D., MORTIMER S. FALK, M.D., AND JOHN H. STOKES, M.D.

One hundred and eleven cases of cardiovascular syphilis were treated with penicillin and, of these, 13 were in congestive heart failure, eight suffered from angina pectoris, and three had a history of coronary occlusion. Except for mild fever in a few instances therapeutic shock was not observed in any of the patients and therapeutic paradox, although sought for, was also not observed. There is evidence to suggest that penicillin has a favorable influence upon cardiovascular syphilis; angina pectoris and congestive heart failure do not contraindicate the use of penicillin in cardiovascular syphilis.

IN 1949[1] we reported the early observations of this group on penicillin-treated syphilitic cardiovascular disease. Although scattered reports of untoward reactions as the result of penicillin treatment of late cardiovascular syphilis appeared in the literature,[2–6] in none of this series were there reactions which could be construed as due to a serious therapeutic shock, although mild fever occurred in some cases. Therapeutic shock or the Jarisch-Herxheimer reaction is a term applied to an exacerbation of the signs or symptoms of the disease in a syphilitic patient in any stage of the disease immediately following treatment with antisyphilitic drugs. Moreover, despite careful observations for therapeutic paradox, nothing definitely classifiable as such was observed within the observation period. Therapeutic paradox was described by Wile[7] and has been attributed to over-rapid healing, with resulting functional imbalance so that the patient is in a worse condition after treatment than before. It was believed any organ may have its function seriously impaired by rapidly induced fibrosis, but insofar as the cardiovascular system is concerned, embarrassment of the coronary circulation as the result of fibrosis around the coronary ostia or the production of aortic insufficiency due to involvement of the aortic ring are two of the complications which were feared.

Later[8] observations were reported on 12 patients with syphilitic heart disease and congestive heart failure in whom penicillin and methods to combat congestive failure were used simultaneously. In this group not only were untoward effects lacking, but the distinct impression prevailed that these patients responded better than most patients with cardiovascular syphilis and decompensation who were treated, as was often the case in the prepenicillin era, with measures aimed only toward combating congestive failure.

Previous to the above reports, Russek, Cutler, Fromer and Lahman[9] and also Tucker and Farmer[10] reported that patients with cardiovascular syphilis tolerated penicillin well. To these have been added the series of Flaum and Thomas,[11] additional cases by Russek, Nicholson and Lohman,[12] Peralta and Casteneda[13] and the experiences of Webster.[14]

MATERIAL AND METHODS

Since the initial reports the series has enlarged to include a total of 111 cases. The purposes of the present study were to determine: (1) To what extent penicillin is tolerated by patients with cardiovascular syphilis, including those with congestive

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(The Penicillin-Syphilis Panel consists of representatives of the Institute, Departments of Neurology, Ophthalmology, Dermatology and Syphilology and Pediatrics, Hospital of the University of Pennsylvania; the Division of Venereal Disease Control, Philadelphia City Department of Public Health; the Philadelphia General and Pennsylvania Hospitals, and the Children's Hospital.)

failure or angina pectoris; (2) by prolonged follow-up studies, to determine: (a) the frequency of therapeutic paradox, and (b) the influence of penicillin treatment upon the subsequent course of cardiovascular syphilis.

criteria mistakes in diagnosis may be made especially in the older age group. A systolic murmur at the aortic area followed by an accentuated and tambour-like second sound in a person under 40, with positive serologic tests for syphilis, and without evidence of hypertension, arteriosclerosis or rheumatic heart disease was considered suggestive evidence of aortitis, especially when the above were associated with a dilated, elongated ascending aorta with or without calcification; those cases with a definite pulsating bulge of the arch of the aorta or its main branches were considered aneurysm. Angina pectoris and paroxysmal dyspnea in this group were considered possible evidence of coronary ostial involvement. In the older age groups with hypertension and/or arteriosclerosis and positive serologic tests for syphilis, the diagnosis of aortitis was extremely difficult and errors in diagnosis were probable, but only a comparatively few cases (table 1) in whom the aorta was far more dilated than expected for the degree of hypertension, were included in this group. Other patients, in whom the signs could not be considered out of proportion to the degree and duration of hypertension, were treated with penicillin but were not included in this study.

TABLE 1

	No. of Cases	Sex		Color		Age Distribution			
		M	F	B	N	0-10	40-50	50-60	60-70
Aortitis	48	33	15	30	18	13	18	10	7
Aortic insuffic.	51	42	9	28	23	5	13	22	11
Aortic insuffic. and aneurysm	9	8	1	5	4	0	2	4	3
Aneurysm	3	3	0	1	2	0	2	1	0

TABLE 2.—*Serologic Data before and after Treatment*

	Aortitis	Aortic Insufficiency	Aortic Insufficiency Aneurysm	Aneurysm
No. of cases	48	51	9	3
STS Positive*				
Before treatment	41	39	8	3
After treatment	34	42	7	3
STS negative				
Before treatment	7	12	1	0
After treatment	11	7	1	0
Change in titer†				
Same	18	13	4	2
Fall	13	20	2	1
Rise	2	3	0	0
Negative before, positive after	1	7		0
No follow-up	3	2	1	0
CNS‡ syphilis	26	17	5	2

* Serologic test for syphilis.

† Change in titer: Rise—increase of two or more titers in quant. titer; Fall—drop of two or more titers in quant. titer; Same—no change or one titer rise or fall.

‡ Central nervous system syphilis.

The cases included in this study were divided into the following 4 groups:

(1) Simple aortitis	48 cases
(2) Aortic insufficiency	51 cases
(3) Aortic insufficiency and aneurysm	9 cases
(4) Aneurysm	3 cases

The pertinent data concerning race, age and sex are listed in table 1. In table 2, are presented the pertinent syphilogic data. We are aware that the diagnosis of simple aortitis is frequently most difficult, and it must be admitted that even with rigid

All cases were hospitalized and were given complete physical examinations before treatment. Laboratory studies included electrocardiogram, fluoroscopic study of the heart, complete blood count, urinalysis, serologic tests for syphilis, and such studies as determination of urea nitrogen and blood sugar, when necessary. Electrocardiograms were made approximately every three days during treatment in 42 of the 111 cases. All the patients were given sodium penicillin in aqueous solution intramuscularly on a round-the-clock schedule until a total dosage of 4,800,000 to 9,600,000 units had been given. In some of the earlier cases the initial doses were small, 500 to 5,000 units every three hours. All the later cases were started on larger doses, 40,000 to 80,000 units every two or three hours until a total of 4,800,000 to 9,600,000 units were given and repeated once if indicated. Follow-up studies were made three months after discharge from the hospital and every six months thereafter, whenever possible. In many cases, especially in

those who had congestive failure, opportunity to follow these patients in the cardiac clinic at frequent intervals was afforded. In every follow-up study, complete physical examination, electrocardiogram, and fluoroscopic study of the heart were made, in addition to serologic studies.

Results

Simple Aortitis

Five of the 48 patients who were considered to have simple aortitis, but who probably had coronary ostial involvement also, had paroxysmal dyspnea and four were improved after treatment; one showed little or no change. One patient who had congestive heart failure continued to have nocturnal dyspnea in spite of measures to combat congestive failure, until relieved by treatment with penicillin, and was free of attacks 12 months later. This case has been reported in detail elsewhere.[8] The other three were free of nocturnal dyspnea when examined 10 months, 14 months and three years after treatment. The fifth patient continued to have attacks after three and one half months. One patient who had suffered a coronary occlusion before penicillin therapy, and who did not suffer from nocturnal dyspnea at the time of treatment, was in congestive failure and had nocturnal dyspnea 58 months after treatment.

Angina pectoris was present in three instances. Two were improved three and one half and 19 months after treatment; the other showed no change after 11 months either in severity or frequency of attacks.

Pertinent data regarding roentgen examination before and after treatment are listed in table 3, and in table 4 are listed the electrocardiographic findings before and after treatment; neither the roentgen or electrocardiographic changes noted after treatment can be considered significant. Electrocardiograms were made every three days during treatment in 17 cases. In 11 the tracings remained unchanged, but in six there were slight but probably not significant changes in the T waves. In three there was an increase in amplitude of the T waves in the limb and/or precordial leads, and in three the T waves became lower but not inverted. In all but one, however, the changes were transient, but in this case the improvement persisted after 42 days.

The aorta was considered abnormal in all cases but no attempt was made to evaluate slight changes in aortic measurements. There was no marked change noted following treatment. We have not observed the development of an aneurysm or aortic insufficiency in a single case.

Table 3.—*Heart Size in 48 Cases of Aortitis*

Before Treatment		After Treatment			
		Same	Larger	Smaller	No follow-up
Normal	22	13	1	—	8
Normal but config. of left. vent. hypertrophy	6	6	—	—	—
Slight enlargement	14	6	3	2	3
Moderate enlargement	4	1	—	—	3
Marked enlargement	2	1	0	1	—

Table 4.—*Electrocardiograms in 48 Cases of Aortitis*

Before Treatment		After Treatment			
		Same	Improved	Worse	No follow-up
Normal	28	17	—	2	9
Myocardial damage	11	2	4	1	4
Left ventricular hypertrophy	6	4	—	1	1
Right bundle branch block	1	1	—	—	—
Left bundle branch block	0	—	—	—	—
Myocardial infarction	2	1	—	—	1

There was one death attributed to pneumonia 12 months after treatment.

Aortic Insufficiency

Nine of the 51 patients with aortic insufficiency had signs of congestive failure and five others were receiving digitalis but no longer showed signs of failure. All were treated with penicillin simultaneously with measures to combat congestive failure, and all left the hospital feeling much improved. In no case was there evidence of therapeutic shock; one patient who also had auricular fibrillation died two months

later from a pulmonary embolus; one died as a result of unknown causes 66 days after treatment, and one after five months as a result of uremia. The others were in a much improved condition 5 to 17 months after treatment, although they continued on digitalis and mercurial diuretics. One patient who did not have signs of congestive failure before treatment developed signs of failure 36 months later, but this was controlled easily by the usual measures to combat congestive failure.

One patient who had subacute bacterial endocarditis was well eight months following treatment.

Five patients had angina pectoris and four were improved 3 to 28 months after treatment. The fifth case was the patient who died from a pulmonary embolus.

Data regarding heart size before and after treatment are listed in table 5 and in table 6 data relating to electrocardiographic findings before and after treatment. Of the nine cases showing marked enlargement, eight suffered from congestive failure. The other was receiving digitalis although he showed no signs of congestive failure. Six of these nine showed diminution in heart size 5 to 17 months after treatment; the remaining three died before follow-up examinations could be made.

Of the 16 whose heart size was normal although the configuration suggested left ventricular hypertrophy, a follow-up study was made in 14 cases. Of these, five showed increase in heart size. Seven of the 11 patients who showed slight cardiac enlargement were studied after treatment and four showed an increase in size of the heart; one of these was the patient with subacute bacterial endocarditis. Of the 15 patients with moderate cardiac enlargement, 10 were followed up; four showed diminution in size of the heart and in six the heart remained the same in size 9 to 17 months after treatment. The most marked improvement in heart size, therefore, was noted in the moderately and markedly enlarged groups. In the latter group all patients were in congestive failure or had a history of failure, and all were treated with digitalis and other measures to combat congestive failure; the diminution in size, therefore, may have been due to the latter measures and not to penicillin.

Electrocardiograms were made every three days during treatment in 20 cases, and in 14 there were no significant changes. In five instances, there were transient T-wave changes in the limb and/or precordial leads; one showed increased amplitude of the T waves and in four the T waves became of lower amplitude or inverted in one or more leads, but all returned to the pretreatment pattern before discharge from the hospital. One patient who had evidence of intraventricular block, developed complete heart block three days after treatment was started, but the electrocardiogram returned to the pretreatment pattern three days later although penicillin was continued. However, he had frequently developed complete heart block for short periods of time before treatment, and penicillin was therefore not considered responsible.

Follow-up study was made in 10 of the 12

TABLE 5.—*Heart Size in 51 Cases of Aortic Insufficiency*

Before Treatment		After Treatment			
		Same	Larger	Smaller	No follow-up
Normal	0	—	—	—	—
Normal but config. of left vent. hypertrophy	16	8	5	—	3
Slight enlargement	11	3	4	—	4
Moderate enlargement	15	6	—	4	5
Marked enlargement	9	—	—	6	3

TABLE 6.—*Electrocardiograms in 51 cases of Aortic Insufficiency*

Before Treatment		After Treatment			
		Same	Improved	Worse	No follow-up
Normal	12	9	0	1	2
Myocardial damage	4	2	2	0	0
Left ventricular hypertrophy	31	18	1	1	11
Right bundle branch block	2	1	0	0	1
Left bundle branch block	2	0	0	0	2

patients whose electrocardiograms were considered normal before treatment; in only one of these patients were there T-wave changes, and these were of the type observed in left ventricular hypertrophy. This patient also showed considerable increase in cardiac area following healing of subacute endocarditis, involving the aortic valve.

In seven cases the soft diastolic murmur of early aortic insufficiency could not be heard on repeated examinations 3 to 40 months after treatment; in three cases the intensity of the murmurs was markedly reduced and they were barely audible. In two patients with wide-open aortic insufficiency the murmurs were markedly reduced three to nine months after treatment, but in the remaining 39 patients with wide-open insufficiency there was no detectable change in the intensity or quality of the murmur.

One elderly negro male with aortic insufficiency, hypertension 220/120, and arteriosclerosis was suspected of having developed an aneurysm of the innominate artery nine months after treatment, and this was at first considered the only instance of therapeutic paradox in this study. However, this patient subsequently died of cerebral hemorrhage, and an autopsy revealed a tortuous and sclerotic innominate artery but no evidence of aneurysm.

Aneurysm and Aortic Insufficiency

There were nine cases in this group. The aneurysm involved the ascending aorta in six instances, the ascending and transverse arch in one, the descending aorta in another, and the innominate artery in another instance.

The heart was normal in size in three cases, slightly enlarged in one instance, moderately in three and markedly in two. Follow-up study was made in six cases and no change in heart size or aneurysm was noted 8 to 38 months after treatment.

The electrocardiogram before treatment showed changes indicative of left ventricular hypertrophy in three, T-wave changes indicative of myocardial damage in two, a healed posterior infarction in one, and in three the tracings were normal. Electrocardiograms were made every three days in five cases but showed no significant changes.

Ten months after treatment there was considerable improvement in one of the tracings showing myocardial abnormality, and it is also of interest that a soft diastolic murmur heard before and during treatment could no longer be heard in this patient on repeated examinations. Three patients were in congestive failure, and also improved under combined treatment. Two of them died subsequently, however, one as a result of uremia 20 months after treatment, and the other after 21 months as a result of unknown causes.

Aneurysm without Aortic Insufficiency

There were three patients in this group. One patient had an aneurysm of the left common carotid artery, one of the ascending aorta and in the third patient the aneurysm involved both the ascending and transverse portions of the arch. The latter patient died 34 days after treatment following operation in an effort to prevent further enlargement of the aneurysm.

The heart was normal in size in one instance, moderately enlarged in another, and in the third case the heart was of normal size but the configuration suggested left ventricular hypertrophy.

The electrocardiogram of the patient with moderate cardiac enlargement showed evidence of left ventricular hypertrophy but was normal in the other two cases.

In two cases electrocardiograms were made every three days during treatment. In one there was no change but in the other there was considerable improvement in amplitude of the T waves.

Follow-up study in the first case 15 months after treatment showed no change clinically or in the electrocardiogram or orthodiagram.

Discussion

During the five years of this study certain facts concerning the use of penicillin in cardiovascular syphilis have become clear, and some of the question marks which loomed so conspicuously six years ago are no longer present. Only time, however, careful clinical study and postmortem examinations will determine

whether a number of impressions gained during these five years, which at present must be labeled "Not Proved," are sound. However, there is suggestive, but by no means convincing, evidence that penicillin has had a beneficial effect in the large majority of patients treated in this series and conversely, there is ample evidence both from our own study and from the literature that harmful effects are rarities. This evidence may be briefly summarized as follows:

1. The reduction in intensity or possible disappearance of the diastolic murmurs in some cases. In seven patients in whom the murmur was the soft type, suggestive of early aortic insufficiency, the murmur could not be heard on repeated examinations after treatment, and in three cases the murmur became barely audible. In no case did the loud, blowing, high-pitched diastolic murmur, suggestive of wide-open insufficiency disappear, but in two cases there was a marked diminution in intensity of the murmur, which could not be explained by a drop in blood pressure, change in cardiac rate or blood count. One may speculate in these instances that the inflammatory process which caused widening of the commissures was still in a reversible stage; if insufficiency were due to dilatation of the ring, the resultant fibrosis of healing was sufficiently great to counterbalance the dilatation. We are aware that this is pure speculation, but the frequency of this finding is strongly presumptive evidence of the validity of our impression that these patients are benefited by penicillin. We have not observed similar results in the prepenicillin era except in cases where the murmur was produced by some hemodynamic factor which was corrected or alleviated.

2. The favorable effect upon patients with paroxysmal dyspnea and congestive failure. Paroxysmal dyspnea was present in five patients with simple aortitis and probable coronary ostial involvement in nine cases of aortic insufficiency and in one of aortic insufficiency and aneurysm, or a total of 15 instances; in all the patients with aortic insufficiency, one with aortic insufficiency and aneurysm and one with simple aortitis but with probable coronary ostial involvement, there were evidences of severe congestive failure. Two other patients with aortic insufficiency and aneurysm had signs of congestive failure but not paroxysmal dyspnea. In these, measures to combat congestive failure were used simultaneously with penicillin.

The group of patients with cardiovascular syphilis and congestive heart failure tolerated combined treatment very well; nevertheless, we do not have sufficient evidence to state definitely that penicillin alters the course or prognosis of patients with cardiovascular syphilis and cardiac decompensation. Because the clinical course and prognosis of this group is frequently altered by many variables such as duration of infection, amount of early treatment, complicating conditions such as hypertension, arteriosclerosis, nephritis and diabetes, or social and economic status, a control group could not be studied especially in view of the paucity of material; furthermore, we were reluctant to deprive a seriously ill patient of a therapeutic measure which, to us, seemed of definite value.

Of the four cases of aortitis with paroxysmal dyspnea, but without signs of chronic congestive failure, paroxysmal dyspnea was relieved by penicillin alone in three instances, but in one case, the symptoms remained unchanged.

One of us (J. E.) treated a patient with aortitis complicated by hypertension and severe congestive failure for several years before this study was undertaken. Although this patient had hypertension, the dilatation of the aorta was so marked and the history of syphilis so definite, that there was little doubt about the diagnosis. Notwithstanding full digitalization, ammonium chloride, a salt-free diet and frequent injections of a mercurial diuretic, nocturnal dyspnea was so incapacitating that resort to one of the morphine derivatives became necessary. Finally, penicillin was advised as a last resort, in full awareness of the cardiologic teaching that it was extremely hazardous to give antisyphilitic treatment in the presence of congestive failure. The favorable response was so dramatic that we were prompted to treat our other patients with congestive failure with penicillin concomitantly with the time-honored drugs for congestive failure; details of this case

and the results of this study have been reported elsewhere.[8] We have lost sight of this first patient, but for 12 months following treatment he was free of attacks of nocturnal dyspnea.

On the other hand, two patients who were free of signs of congestive failure developed nocturnal dyspnea, but in neither case could treatment be implicated as a possible causative factor because of the long interval after treatment. One patient with simple aortitis who had previously suffered a coronary occlusion developed paroxysmal dyspnea and other evidences of congestive heart failure 58 months after treatment; the other, a patient with aortic insufficiency, was much improved for three years, but then developed congestive heart failure and nocturnal dyspnea. His symptoms were easily controlled with digitalis and weekly injections of a mercurial diuretic.

3. Improvement under penicillin in some cases of angina pectoris. Eight patients, five with aortic insufficiency, and three with simple aortitis, suffered from angina pectoris. Four of the former group and one patient with aortitis were free of angina pectoris or markedly improved after treatment in that the frequency and severity of attacks were reduced; one with aortitis was only moderately improved, and two, one with aortic insufficiency and the other with simple aortitis, showed no improvement. We are aware that, as a group, some of the patients comprising this study were very unreliable and open to suggestion, but in two there was considerable improvement in the electrocardiogram, and in another the soft diastolic murmur could not be heard after treatment. Thus there is suggestive objective evidence that angina pectoris may be favorably influenced by penicillin treatment and that angina pectoris is not a contraindication to treatment with penicillin.

It might be added that three other patients who had recovered from coronary occlusion but who did not have angina pectoris, were treated with penicillin without untoward symptoms, and another patient, not included in this study, who suffered from an acute myocardial infarction, was treated with penicillin because of a complicating pneumonia without untoward reaction.

4. The subjective improvement experienced by most patients supports the efficacy of penicillin. The feeling of well being which is manifested by these patients and the appearance of improved health on leaving the hospital was striking. Good food, frequent bathing, a clean bed and a roof over their heads were undoubtedly contributing factors of more than minor significance to some, but the frequency with which the improvement continued for periods of months and years left little doubt that penicillin was also a factor.

It must be emphasized that even if the ultimate aim of treatment is achieved—cure of the syphilitic infection—the patient, unless treated before complications have occurred, is left with a badly damaged heart or aorta, and this may eventually lead to death. Aneurysms may become larger and cause pressure symptoms or rupture, although the active syphilitic infection has been cured. Patients with partial occlusions of the coronary ostia, may continue to have angina pectoris and nocturnal dyspnea, and those with wide-open aortic insufficiency may continue to show progressive left ventricular hypertrophy and eventually heart failure. There are, however, at present no reliable data to indicate that the infection in cardiovascular syphilis has been eradicated by treatment with penicillin. Although a great deal of information regarding heart size and electrocardiograms before and after treatment has been accumulated, there are so many complicating factors that cannot be evaluated, such as arteriosclerosis, hypertension, drugs, congestive failure, type of work, or social position, which may influence heart size and the electrocardiogram, that they cannot be used to gage accurately the results of penicillin therapy in syphilitic aortitis and its complications. Comparison of measurements of the diameter of the aorta is admittedly inaccurate, and unless there are marked differences they cannot be considered as significant. The available data, however, would indicate that treatment of cardiovascular syphilis with or without angina pectoris or congestive failure with penicillin, can be carried out without fear of serious reaction, and that therapeutic paradox, if it does occur, is a rarity.

Sudden death from syphilitic aortitis is not

uncommon and may be due to a rupture of an aneurysm or to coronary ostial involvement. We can recall a number of these catastrophes, sometimes when syphilitic aortitis was not suspected and before any treatment was instituted. Therefore, in a study comprising a large number of cases of cardiovascular syphilis over a span of years, a sudden death, totally unrelated to treatment but merely coincidental, is probable. Recently we observed a young negro who had a very large heart with loud to and fro murmurs over the base, and a marked and diffuse dilatation of the aorta on roentgen examination. In spite of negative serologic tests the findings were so suggestive of syphilitic aortitis with aortic insufficiency that treatment with penicillin was instituted. He had complained of paroxysmal dyspnea on admission but was much improved on rest in bed, digitalis and mercurial diuretics. Five days after penicillin was started his symptoms became markedly exaggerated and death occurred suddenly during one of the attacks of nocturnal dyspnea. This case strongly suggested that the increase in symptoms and finally death was due to penicillin. Postmortem examination, however, disclosed that not only was penicillin *not* the cause of his death, but there was no pathologic evidence of syphilitic aortitis. The diffusely dilated aorta and murmur were due to a dissecting aneurysm starting in the beginning of the ascending aorta; there was also double abdominal aorta, probably congenital.

To attribute death unequivocally to penicillin without postmortem evidence is contrary to known clinical facts. Theoretically swelling of a syphilitic lesion near the coronary ostia may cause an increase in angina pectoris or sudden death during treatment, but we have not observed either complication in our series. Undoubtedly, many thousands of patients with syphilitic aortitis have been treated with penicillin because of unrelated infections long before a diagnosis of syphilis or its complications was suspected, but we have not observed any sudden increase in sudden deaths in infectious diseases, nor have we been aware of any reports of an unusual number of deaths in infections treated with penicillin. If such were the case, then treatment of infections with penicillin would be hazardous unless syphilitic aortitis were ruled out, a procedure which would require hours of ill-afforded time, even if the diagnosis could be made with certainty. We were encouraged to start treatment with large doses of penicillin because we observed several surgical cases who had syphilitic aortitis, but in whom this diagnosis was not suspected, and who were given large doses of penicillin without therapeutic shock. The lack of reaction to such a powerful spirocheticidal agent as penicillin and conversely the frequent reactions to arsenic suggests that the latter was not due to rapid destruction of spirochetes, but to vasculotoxic action of the arsenicals.

Therapeutic paradox, although sought for, was not observed. We have not observed a single patient who developed aortic insufficiency or aneurysm after treatment; there is a possibility that aortic insufficiency may develop at a later date in some of our cases as the result of stretching of an already damaged ring or as the result of hypertension, but this cannot be considered a therapeutic paradox and may be due to a natural deterioration of a damaged aorta. Angina pectoris may subsequently occur not only as a result of an increase of fibrosis around the ostia, the result of healing, but as the result of coronary disease, unrelated to syphilis, especially in the old age group, with or without hypertension.

The lack of therapeutic shock, except for slight fever, would argue for treatment with penicillin in cases of syphilis with doubtful cardiovascular findings. It is hoped that delayed action penicillin will be as efficacious as aqueous penicillin in the treatment of cardiovascular syphilis, and that treatment may, therefore, be carried out on an ambulatory basis. We have already treated 13 patients with severe cardiovascular syphilis with procaine penicillin on an ambulatory basis without untoward symptoms; details of these cases will be included in a later report.

Summary

1. We have treated 111 patients with cardiovascular syphilis with penicillin.

2. At first we started with very small doses, fearing (a) therapeutic shock which might close

off a stenosed coronary orifice or, (b) therapeutic paradox which, despite healing of the lesions, might give rise to mechanical difficulties as a result of the scars of healing.

3. As time went on, we became bolder, and started therapy with the full dose of 40,000 to 80,000 units of aqueous penicillin every two or three hours until 4,800,000 to 9,600,000 units were given.

4. We never saw evidence of either therapeutic shock or paradox, although a few patients developed a mild fever.

5. As to the favorable effects of penicillin in cardiovascular syphilis, it is reasonable to believe that they will occur in some patients. It was difficult to measure the benefits in our patients because there were no controls. Moreover, in addition to penicillin, we used the other recognized methods of treatment in those patients with signs or symptoms of congestive heart failure.

6. The beneficial effects which we thought we observed were: (a) Some patients with nocturnal dyspnea and symptoms of congestive heart failure improved to a degree we did not expect from therapy other than penicillin. This also occurred in a few patients with anginal pain. (b) In a few patients, a soft aortic diastolic murmur seemed to disappear, or a loud murmur became softer.

7. The main point we wish to stress is that it does not appear to be dangerous to treat patients with cardiovascular syphilis with penicillin.

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The Inhibition of Coronary Atherosclerosis by Estrogens in Cholesterol-Fed Chicks

By R. Pick, M.D., J. Stamler, M.D., S. Rodbard, M.D., Ph.D., and I. N. Katz, M.D.

Chronic administration of estrogens parenterally inhibits coronary atherogenesis in cockerels fed a cholesterol-supplemented diet, although no such prophylactic effect was observed against aorta atherogenesis. This protection of the coronary vessels is associated with depression of the plasma total cholesterol–lipid phosphorus ratio toward normal levels consequent upon estrogen-induced hyperphospholipemia.

CORONARY atherosclerosis occurs with significantly greater frequency in the human male than in the female.[3, 4] Little is known concerning the basis for this sex differential in susceptibility to coronary atherogenesis. In an attempt to clarify this problem experimentally, we studied the effects of estrogen administration on atherogenesis in the coronary arteries and aorta of cholesterol-fed cockerels. Plasma lipid patterns were simultaneously analyzed in order to ascertain whether any observed morphologic effects might be correlated with concomitant lipid alterations.

Methods

Forty-five 1 day old Hy-line cockerels were obtained from a commercial hatchery and reared in a battery brooder. They were fed commercial chick starter mash until they were 7 weeks of age. They were then divided into three groups: Group 1 (control) received mash supplemented with 2 per cent cholesterol and 5 per cent cotton seed oil. Group 2 (experimental) received the same diet plus daily injections of 1 mg. estradiol benzoate (Progynon B, Schering).* Group 3 received plain a diet of mash without cholesterol supplement, and daily injections of 1 mg. estradiol benzoate.† Blood samples were taken and groups of chicks sacrificed at 12, 15 and 20 weeks of age (5, 8 and 13 weeks on the experimental regimens, respectively). Individual blood samples were analyzed for total cholesterol and for lipid phosphorus by the methods of Schoenheimer and Sperry[8] and of Man and co-workers,[9] respectively. At autopsy the hearts and great vessels were inspected for gross atherosclerotic plaques. The lesions were recorded graphically on special forms and graded grossly 0 to 4 according to criteria previously described.[7, 10] The hearts were then fixed in 10 per cent formaldehyde. Two blocks were cut from each heart; two frozen sections were then cut from different levels of each block and these were stained with Sudan IV for lipids. When no coronary atheromatous lesions were found in these sections, eight further blocks were cut from these hearts and treated similarly. The hearts were described as either positive or negative for microscopic atherosclerosis. No attempt was made to grade the lesions. A heart was described as negative when no artery in 20 examined sections showed a lipid-containing intimal lesion.‡

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Some of the data of these experiments were presented before the September, 1950 meeting of the American Physiological Society[1] and the November, 1951 meeting of the American Society for the Study of Arteriosclerosis.[2]

* We are grateful to Dr. Abbott W. Allen of the Schering Corp., Bloomfield, N. J., for the generous quantities of Progynon B which he kindly supplied for these experiments.

† This latter group confirmed previous findings concerning the effects of estrogenic substances in birds fed normal diets.[5–7] These data are not relevant to the present study.

‡ At the 20 week sacrifice (13 weeks on the experimental regimen), slight lipid accumulations were present in the media of several coronary arteries of three birds of group 2. This lipid was uniformly confined to the media; in no case was it present in the intima. The intima appeared normal, no fibrotic changes were observed in the media, the vessel was not thickened and the lumen was not narrowed. These lipid accumulations, therefore, were not considered to be atheromas.[7] Hearts with an occasional artery exhibiting only this medial change were considered negative for coronary atherosclerosis.

Results

1. Pathologic Findings

The gross and microscopic findings at the three periods of sacrifice were essentially similar and are therefore described together.

Aorta: Gross atherosclerosis in the aorta was present in 100 per cent of birds of both groups. The mean grading for gross aorta lesions was 3.1 and 3.9 for groups 1 and 2 respectively. Thus there were no significant differences between the two groups in incidence and severity of aorta atherosclerosis. In both groups, the gross and microscopic appearance of these lesions was typical of cholesterol-induced atherosclerosis.[7, 11, 12] The only noticeable gross difference was a more vividly yellow color of the lesions in the estrogen-treated chicks.

Coronary Arteries: The hearts appeared grossly normal. On microscopic examination, however, a significant difference was noted between the two groups. All group 1 chicks (receiving cholesterol without estrogens) showed a marked degree of coronary atherosclerosis. Lesions varied from early, subendothelial lipid infiltrations to massive atheromatous lesions virtually occluding the lumen of the vessels. Some lesions also showed sclerotic changes, that is, fibrosis and calcium deposition. In contrast to these findings, only 4 of 12 birds in group 2 (cholesterol-fed, estrogen-injected) exhibited coronary lesions.

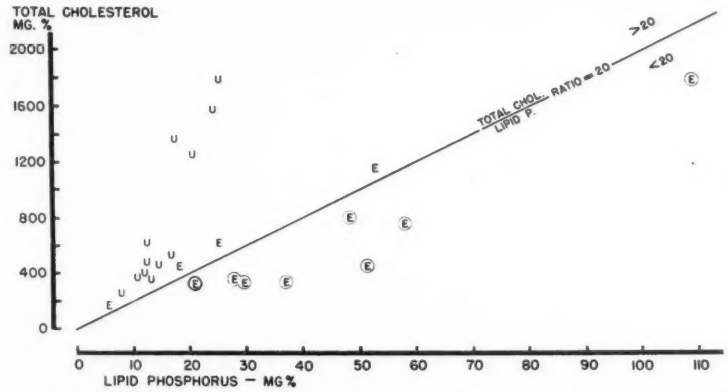

FIG. 1. The relationship of the plasma cholesterol (C) and lipid phosphorus (P) to the presence of coronary atherosclerosis. Values are simultaneous (C and P) at the time of sacrifice. Ordinates represent the total plasma cholesterol level in mg. per 100 cc. The abscissas represent the lipid phosphorus in mg. per 100 cc. The U's represent chicks fed 2 per cent cholesterol but not treated with estrogens. The E's represent chicks on the same diet but receiving 1 mg. estradiol benzoate intramuscularly daily. The circled E's are cases without coronary atherosclerosis. The diagonal line represents a C/P ratio of 20. Symbols above the line have a ratio greater than 20, while those below the line have a ratio less than 20.

TABLE 1.—*Effects of Estrogen Administration on Plasma Lipids and on Coronary Atherosclerosis in Cholesterol-fed Chicks*

	No. of chicks*	Total cholesterol mg.%	Lipid P† mg.%	C/P ratio‡	% Coronary lesions
Group 1: 2C-O§	13	895¶ 380–1800‖	17 8–25	47 32–77	100
Group 2: 2C-O + estrogen	12	742 129–1800	47 6–109	16 9–25	33

* Two birds in the 2C-O group and 3 birds in the 2C-O + estrogen group died during the experiment. No plasma lipid determinations were done, therefore they are not included in the series.

† Lipid P = lipid phosphorus.

‡ C/P ratio = cholesterol/lipid phosphorus ratio.

§ 2C-O = diet of mash supplemented with 2 per cent cholesterol and 5 per cent cottonseed oil.

¶ mean value.

‖ Range.

2. Biochemical Findings

The data on plasma lipids are summarized in table 1. The mean value for total cholesterol in group 1 (895 mg. per 100 cc.) was slightly but not significantly higher than in group 2 (742 mg. per 100 cc.). In contrast to the similar plasma cholesterol levels, the two groups exhibited significant differences in plasma lipid phosphorus concentrations. Whereas the mean lipid phosphorus level in group 1 was 17 mg. per 100 cc., in group 2 (cholesterol-fed, estrogen-injected) it was 47 mg. per 100 cc. Correspondingly, the total cholesterol–lipid phosphorus (C/P) ratios were 47 and 16,* respectively, that is, the estrogen-treated, cholesterol-fed birds had C/P ratios near the normal level, whereas the group 1 cockerels had markedly elevated ratios.

3. Pathologic-Biochemical Correlations

A close relationship was found between C/P ratio and the occurrence of coronary atherosclerosis (fig. 1). Thus, all birds of group 1, with markedly elevated C/P ratios, had coronary atherosclerosis.* In group 2, chicks with C/P ratios less than 20 were uniformly free of lesions. Whenever the dosage of estrogen was inadequate to keep the C/P ratio depressed below 20,† coronary atherosclerosis was present (fig. 1). This occurrence of coronary atherosclerosis was not related to the level of total cholesterol (table 1). This fact emerges even more clearly when data on individual chicks of group 2 are considered. Thus, one estrogen-treated bird with a cholesterol level of 1800 mg. per 100 cc., but a C/P ratio of only 16 had no coronary lesions; another injected chick with a cholesterol of only 460 mg. per 100 cc., but a relatively high C/P ratio of 25 had distinct coronary lesions.

Discussion

The data of these experiments demonstrate clearly that estrogens may prevent coronary atherogenesis in cholesterol-fed cockerels*. These findings are particularly significant in view of the well-known sex difference in human susceptibility to coronary atherosclerosis. Thus, especially before age 40, human males are victims of coronary disease far more frequently than females.†[3, 4] In the latter (postclimacteric) decades of life, the incidence of coronary atherosclerosis in the two sexes becomes similar. Hitherto these findings have been unexplained. The present experiment indicates that estrogenic activity may play an important role in protecting the human female against coronary atherogenesis.

Our findings further suggest that this prophylactic effect of estrogens may depend on their ability to restore cholesterol-phospholipid ratios to normal despite persistent hypercholesterolemia. Data obtained by other workers support this possibility. Thus, studies on patients with chronic biliary xanthomatosis led Ahrens and Kunkel to the conclusion that elevated C/P ratios are key factors in atherogenesis.[13] Gertler and co-workers found that coronary atherosclerosis in young men is correlated with elevation of C/P ratios.[14] Further, Eilert recently demonstrated that estrogens can lower C/P ratios of humans.[15] These clinical findings, although fragmentary, all support the thesis that elevated C/P ratios have significance in the pathogenesis of atherosclerosis. Further, they suggest that estrogenic activity, by depressing C/P ratios to normal levels, may be a factor in the prophylaxis of coronary atherosclerosis in sexually mature females.

Laboratory evidence supporting this concept is also available. Thus, Kellner and associates[16] and Duff and Payne[17] showed that aorta atherogenesis is inhibited in hypercholesterolemic rabbits with normal C/P ratios. In

* The normal C/P ratio for cockerels is 12-13.

† The depression of the C/P ratio by estrogens is a consequence of the pattern of hyperlipemia they induce, that is, predominantly a hyperphospholipemia, in contrast to the predominant hypercholesterolemia of cholesterol feeding.

* Previously Ludden, Bruger and Wright reported that estrogens depressed hypercholesterolemia and aorta cholesterosis in intact cholesterol-fed female rabbits.[19] No consistent effects were observed in male animals. Studies on aorta and coronary atherosclerosis, and on plasma phospholipids were apparently not done.

† This decreased susceptibility to coronary atherosclerosis is not observed in women with diabetes mellitus.[3]

contrast to these findings in rabbits, we observed no correlation between C/P ratios and *aorta* atherogenesis in cockerels.* However, a correlation between C/P ratios and *coronary* lesions was definitely demonstrated in the present experiment.

Finally, one additional significant fact clearly emerges from this experiment, namely, that no necessary relationship exists between atherogenesis in the aorta and coronary arteries. The prevention of lesions in the coronary arteries by estrogens, in the absence of any prophylactic effect against aortic atherosclerosis, makes this principle clear. It becomes apparent that the coronary arteries differ from the aorta in susceptibility to atherosclerosis. This difference in susceptibility of the various vascular beds is also present in man.[18] Hence, it may be concluded that atherogenesis does not proceed according to the same biologic laws in different arterial beds.

These facts warrant the further conclusion that experimental studies of atherosclerosis should not be confined to aorta pathology. In order to elucidate the laws governing atherogenesis in the coronary and cerebral arteries (sites of lesions causing greatest human morbidity and mortality), these particular vessels must be studied experimentally. It can no longer be assumed that laws of atherogenesis in the aorta apply equally well to the coronary and/or cerebral vessels.

Summary

1. Estrogen administration inhibited coronary atherogenesis in cockerels fed a cholesterol-containing diet.

2. This protection of the coronary vessels by estrogen was associated with changes in total cholesterol - lipid phosphorus (C/P) ratios. Thus, all estrogen-treated, cholesterol-fed birds with C/P ratios below 20 were uniformly free of lesions. In all chicks with a C/P ratio above 20, coronary atherosclerosis was present, whether or not estrogen was injected.

3. Estrogen failed to exert any prophylactic effect against atherosclerosis of the aorta in any of the birds.

4. Since the two arterial beds examined in this experiment showed different atherogenic responses to a given procedure (cholesterol feeding plus estrogen injection), it becomes apparent that atherogenesis does not proceed according to the same biologic laws in different vascular beds.

* In addition to the present study, previous experiments yielded similar negative results.[7]

Acknowledgments

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The Blood Flow through the Calf of the Leg during Acute Occlusion of the Femoral Artery and Vein

By JOHN T. SHEPHERD, M.D., M.Ch.

The calf blood flow has been studied in the human subject before and during acute occlusion of the common femoral artery and vein. The results suggest that the concomitant venous occlusion has a detrimental effect on the development of the collateral circulation.

OPINION is divided on the effects of concomitant venous ligation on the nutrition of the limb following injury to the main artery.[2–16, 18–20] In the present investigation the calf blood flow has been studied in the human subject following acute occlusion of the common femoral artery and vein, and evidence is presented which suggests that the simultaneous venous occlusion has a detrimental effect on the blood flow and nutrition of the limb.

METHODS

A mechanical compressor was used to occlude the artery and vein. The maximum combined width of these vessels, measured post mortem, in 17 male subjects was 2.7 cm. The compressor consisted of a hinged horizontal arm fastened at one end to a table; a wooden block 5 cm. by 3.5 cm. surmounted by a 1.5 cm. thick rubber pad was attached to the under surface of the free end of this arm, and this pad was centered as nearly as possible over the artery and vein. A 9.5 Kg. weight, placed directly over the wooden block, was used to occlude the vessels.[17] Blood flows were recorded through the calf of the leg by means of venous occlusion plethysmography before, during and after application of compression.[1] The subjects were all healthy males, age 19 to 30 years.

RESULTS

Resting calf blood flows were recorded and when these became stable the compression was applied to the femoral artery and vein and the calf flow again determined. An immediate decrease in flow to about one-sixth of the resting value occurred on application of compression and this was followed by a rapid recovery, the blood flow returning to approximately its previous resting level in one half to six minutes (average two minutes). The flow remained more or less stable for the next two and one-half to seven and one-half minutes and then decreased throughout the remainder of the period of compression (fig. 1*A*). Compression of the vessels was not usually maintained for longer than 10 to 11 minutes, as after this time it became painful. This paper deals only with the final decrease in flow which was observed in 13 out of 15 subjects tested.

At this stage it was observed that there was an increase in calf volume when both artery and vein were occluded (fig. 1*C*) and as the superficial veins were distending during the period of compression, there seemed little doubt that the increase in calf volume was due to a rise in venous pressure. Estimations of venous pressure were made on six subjects. During compression of the femoral vessels the pressure in the long saphenous vein gradually rose to about 50 mm. Hg (fig. 1*B*). As the collecting pressure used in the recording of the blood flow was 75 mm. Hg, the observed decrease in blood flow was not the result of using too low a collecting pressure.

The rise in venous pressure was due solely to occlusion of the femoral vein and not to obstruction of the collateral venous return by pressure against the couch. This was shown by the following experiment carried out on six of the subjects. Using a compressor with a central fulcrum, it was possible to occlude the artery and vein with the subject in the prone position in order to compare the increase in calf volume

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with that obtained in the same subject in the supine position. The marked similarity of the volume changes in the two positions made it clear that the increase in calf volume and the rise in venous pressure resulted from the inability of the collateral venous circulation to cope with the collateral arterial inflow when the femoral vein was occluded.

It was now necessary to decide whether the observed decrease in blood flow represented a

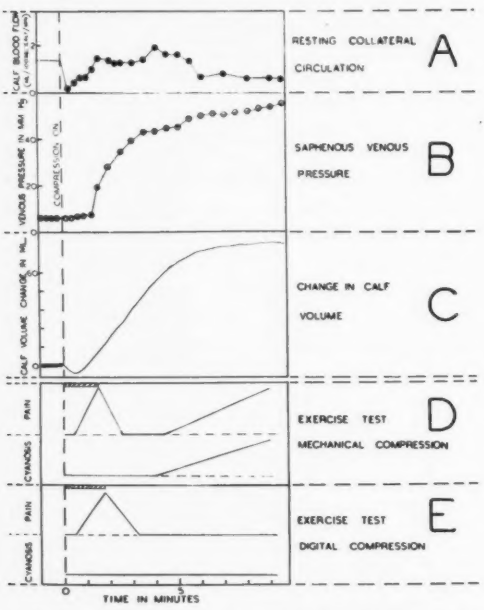

FIG. 1. Results of a typical experiment. The dotted line indicates the application of compression to the femoral vessels. In *A* the blood flow to the left of this line is the average calf flow through the normal circulation. In *D* and *E* the hatched rectangles represent the period of exercise.

true decrease, or an apparent one due to a fault in the method of recording. That is, the plethysmographic method, which depends on accommodation of arterial inflow in the vessels of the limb, may have failed to register accurate flows when the veins and other vessels were already partially distended.

If this were a true decrease in blood flow, then a reactive hyperemia should follow the removal of compression and the more marked the decrease the greater should be the resultant hyperemia. The blood flow through the calf after compression of the femoral vessels was therefore measured and compared over a similar period of time with the blood flow through the calf immediately preceding the period of compression. In figure 2 the abscissa represents the calf blood flow after compression expressed as a percentage of the calf blood flow before compression, and the ordinate represents the

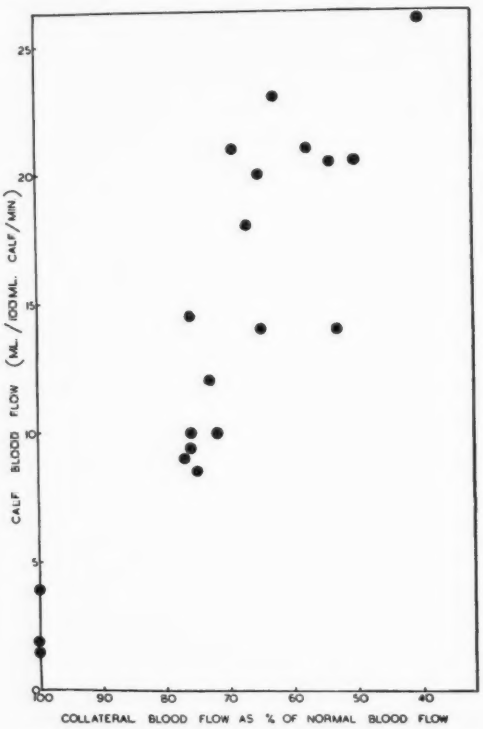

FIG. 2. This shows that the lower the ratio of calf flow after occlusion of the femoral vessels to calf flow before compression (abscissa) the greater is the peak blood flow on removal of compression (ordinate). Results of 20 experiments on 15 subjects.

peak blood flow obtained on removal of compression. It is clear that the lower the percentage the calf flow after compression of the femoral vessels is of the flow before compression, the greater is the resultant hyperemia.

A further analysis made it clear that little if any of this debt was incurred during the initial decrease in calf blood flow immediately after the application of compression, as most

of this had been repaid before the terminal decrease commenced. It seems, therefore, that the rise in venous pressure which follows the venous occlusion causes a true decrease in the collateral blood flow to the calf.

Some workers agree that a rise in venous pressure following concomitant venous occlusion may decrease the blood flow, but they argue that this decrease may be more than compensated by a more homogeneous distribution of the blood in the limb.[2]

To see if any compensation for the decrease in flow occurred in the present series a further test was performed. The weights were applied to the femoral artery and vein and the subject immediately began to plantar and dorsiflex the foot at the rate of one flexion and extension per second. For approximately half a minute from the start of the exercise no pain was felt in the limb. Then a deep seated pain was felt in front of the ankle and occasionally extending upward for a short distance into the extensor compartment of the leg. As the exercise continued the pain steadily increased in severity for about one minute. It then became unbearable so that the exercise had to be stopped. On discontinuing the exercise the pain diminished and completely or almost completely disappeared. Now followed a period of half a minute to three minutes of complete or almost complete freedom from pain. Finally the pain reappeared at the previous site even though exercise was not recommenced, steadily increased in severity, once again becoming intolerable, at which point compression was removed. Just before pain reappeared venous distension was obvious and cyanosis commenced and gradually increased in intensity (fig. 1*D*).

These results confirm the previous findings that a true decrease in blood flow occurred after the collateral circulation had been established for a short period. In addition the return of the pain showed that this decrease was not compensated by keeping the blood longer in the tissues or by a more homogeneous distribution of blood in the limb. In order to show that these results were due to compression of the concomitant vein, it was decided to repeat this test, using digital compression, in an endeavor to occlude the artery only, leaving the vein completely or almost completely patent. This type of compression was adopted in preference to moving the mechanical compressor more laterally in an attempt to occlude the artery only, as it was felt that the sensitive digital compression offered a more reliable and constant method of producing a pure arterial occlusion, especially as the subjects chosen for this test had easily palpable femoral arteries.

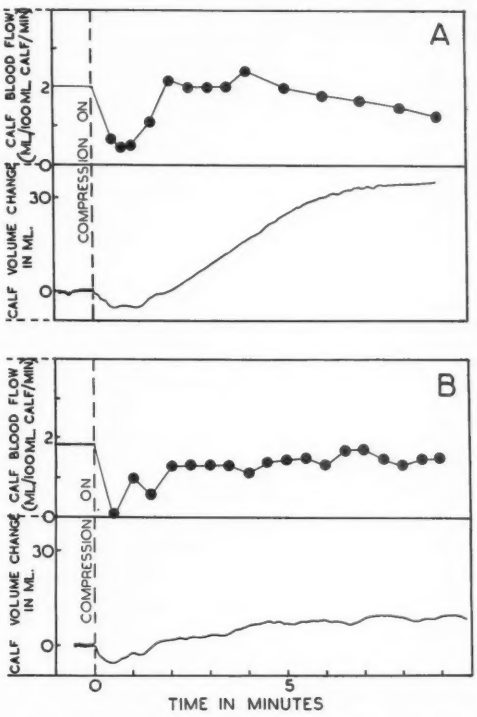

FIG. 3. *A*. Occlusion of femoral artery and vein. *B*. Occlusion of femoral artery with only partial occlusion of the femoral vein.

It was found that the onset of the pain, its situation and maximum intensity coincided with the previous tests but that following the cessation of exercise, the pain decreased as before, died away completely and did not return. There was no venous distension or cyanosis (fig. 1*E*). In addition, in some cases this test was repeated with digital compression of both artery and vein, and results similar to those of mechanical compression were obtained.

Finally it might be argued that the decrease in collateral blood flow was not the result of the rise in venous pressure but was due to reflex vasoconstriction as a result of the pressure of the weights on the femoral vessels. The following observations suggest that reflex vasoconstriction was not responsible.

1. In some of the 13 subjects, who had a small amount of subcutaneous fat in the inguinal region, moving the compression pad further laterally in an attempt to leave part of the femoral vein unoccluded while still occluding the femoral artery resulted in no decrease in blood flow and little or no increase in calf volume (fig. 3).

2. There was no evidence of contralateral reflex vasoconstriction, the flow through the normal circulation in the opposite calf being unchanged during the period of compression.

Discussion

All who are in favor of ligating the concomitant vein following injury to main arteries are agreed that the resulting benefit is dependent upon the production of a partial venous obstruction in the limb concerned. The essential question to be answered is whether following arterial occlusion any benefit can be conferred upon the nutrition of the limb by producing a partial venous obstruction.

Holman and Edwards[6] have suggested that the rise in venous pressure following venous ligation would increase the blood flow through the limb. This has been repudiated by Brooks,[3] Wilson[20] and others. In the present investigation it was found that the extent of the venous obstruction following the occlusion of the femoral vein near its termination led to a marked decrease in collateral arterial inflow in the 5 to 10 minute period following the occlusion.

It could be argued that the rise in venous pressure, while decreasing the blood flow, may be more than compensated by permitting increased interchange of nutritious substances between blood and tissues, first as a result of blood remaining longer in contact with the tissues[8, 9] and second on account of the action of the increased intravascular pressure keeping more capillaries open, and thus facilitating nutritious exchange.[2] The decrease in flow in the present experiment did not appear to be compensated for in this way, as evinced by the return of pain in the exercise test, when the artery and vein were both compressed.

Summary

1. The calf blood flow has been studied in the human subject for 10 minutes during acute occlusion of the common femoral artery and vein.

2. After an initial decrease the calf blood flow rapidly returns to approximately the level present before occlusion, and then decreases again. This latter decrease is due to the rise in venous pressure which results from the occlusion of the femoral vein.

3. The decrease in calf flow due to the rise in venous pressure is not compensated by other changes accompanying the increased venous pressure.

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CLINICAL PROGRESS

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Associate Editor: A. STONE FREEDBERG, M.D.

Hypertension and the Problem of Vascular Homeostasis

By IRVINE H. PAGE AND A. C. CORCORAN

FIFTY YEARS ago hypertension was not a clinical problem. When it was thought of at all, it seemed to be a providential compensation for diffuse structural narrowing and rigidity of small vessels due to "arteriocapillary fibrosis." The incidence and magnitude of the problem began to be appreciated only some thirty years ago when it was generally recognized that hypertension could be discovered in people whose small vessels and circulation generally were structurally intact. Essential hypertension was defined as a clinical entity. By definition, it had no cause, or was "constitutional," so that none but the very enthusiastic or faintly dishonest discussed the possibility of either understanding or curing it. Research was sporadic and speculative. Animal experiments dealt only with acute changes in arterial pressure. Clinical hypertensive disease had no experimental analogue.

This discouraging state changed some twenty years ago when two forms of experimental hypertension were established in animals. The one was neurogenic and resulted from section of the sino-aortic depressor nerves. The other was renal and was elicited by partial compression of the renal artery, or, more recently, by perinephritis.[1, 2] Hypertensive disease has also been produced in rats by administration of desoxycorticosterone and sodium salts, of crude pituitary powder and of growth hormone.[3] The development of means of sustaining life after nephrectomy has resulted in convincing demonstrations of postnephrectomy hypertension in dogs and rats. A neurogenic hypertension has also been obtained by repetitive irritation of the floor of the fourth ventricle. Thus, the experimentalist has been provided with means of studying neurogenic, renal and endocrine mechanisms in hypertension.

The availability of these experimental diseases intensified research into causes and mechanisms, and has led to an analysis of cases of clinical hypertension which is much less perfunctory than the custom was a few years ago. The discovery of hypertension of ascertainable origin and remediable nature has saved the lives of some hundreds of patients. But the problem extends to the millions. In the overwhelming majority of cases, hypertension is still essential and its treatment in a large degree expectant, symptomatic and, in a word, unsatisfactory.

So many facts have now accumulated in the research pool—certainly too many to be considered in any detail—that it is at least opportune from time to time to arrange some of them into patterns which point to pathways which seem to promise most in the research of the future. Such is the aim of this report.

The basic mechanism of essential hypertension is an increase in arteriolar resistance, coupled with an increase in the force of the heart's beat. Associated phenomena in uncomplicated cases are maintenance of cardiac output and peripheral blood flow at approximately normal levels. The problem centers on those factors which directly or indirectly affect arteriolar resistance and, especially, those which

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increase it. These can be grouped as (a) vasomotor, (b) humoral, and (c) possibly also intrinsic changes in the smooth muscle of the arterioles. Since these last have not been seriously studied, however, the discussion must center on the former two categories.

(A) Vasomotor Mechanisms

The several areas in the brain and brain stem at which appropriate stimulation results in changes in arterial pressure and the caliber of arterioles, of which the best defined is the medullary center, are probably more accurately described as aggregates of cells with direct vasomotor outflow than as discrete centers. There is certainly a very widespread distribution of cells which can influence vasomotor function; the centers themselves are functionally interdependent and responsive also to a variety of other controls, from the cortex and thalamus, from respiratory centers, from central and peripheral chemo- and baroreceptors and from substances which reach them in the blood.[4]

The major pathways of pressor and vasoconstrictor discharge from the cerebral pressor centers leads through the cells of the lateral horn of the cord, the dorsolumbar and peripheral sympathetic ganglia to sympathetic vasomotor neurons and the adrenal medulla. Passage of impulses through the ganglia seems to be accomplished by release of acetylcholine around the terminal neuron. Ganglionic transmission is therefore damped or abolished by substances which, like tetraethylammonium (TEAC) seem to compete with acetylcholine at this point. Peripherally, the discharge is apparently accomplished by release around cells in the vessel wall or into adrenal venous blood of a mixture of adrenaline and noradrenaline.[5]

Whereas adrenaline is the major component of normal adrenal medullary secretion, the material released at vasomotor nerve endings is probably in larger measure noradrenaline. This varying proportion in the distribution of adrenergic neurohumors accords teleologically with the fact that noradrenaline is a more consistent vasoconstrictor substance than adrenaline, while adrenaline has more powerful specific metabolic effects. Thus, adrenaline, which is the methylated derivative of noradrenaline, has more effect on heart muscle, so that tachycardia and palpitation characterize its action. In appropriate dilutions and in some areas, such as skeletal muscles, it can be a vasodilator, which apparently noradrenaline cannot be. Adrenaline is also more glycogenolytic and a more potent stimulus of metabolic rate and ACTH release. Pharmacologically, it is the more susceptible to adrenergic blocking agents, such as the benzodioxanes, chlorethylamine and imidazoline derivatives. Hemodynamically, small doses of adrenaline increase cardiac output and may decrease over-all peripheral resistance, although regionally, as in the kidney it usually increases peripheral resistance by causing arteriolar constriction. Equipressor doses of noradrenaline consistently increase both total peripheral and regional resistance. The functional pattern noradrenaline induces is more like that of essential hypertension than that caused by adrenaline; this characteristic has been suggested as a partial explanation of the syndrome which results from the presence of pheochromocytomas, the secretion of which is principally composed of noradrenaline.

As far as essential hypertension is concerned, a corollary of the hemodynamic properties of noradrenaline is that sympathetic vasomotor participation in its mechanism and maintenance must be more seriously considered than that of adrenaline and that thought be given to the possibilities and results of its central inhibition or peripheral blockade. The demonstration, in other fields of study of nervous function, that reverberating arcs may sustain a discharge, as in causalgia or the sympathetic neurovascular dystrophies, suggests that the functioning of afferent pathways should be brought into question as well, for these have not been sufficiently explored.

On the efferent side, the assumption that increased vasomotor discharge is a fundamental mechanism in essential hypertension has underlain the surgical treatment of this condition of adrenal denervation, dorsal and dorsolumbar and total sympathectomies and the more recent studies of the actions and uses of agents which cause peripheral blockade, either ganglionic (TEAC, hexamethonium) or adrenergic. The

transient and, in the case of the operations, sometimes lasting decreases of pressure thus obtained have been advanced as evidence that essential hypertension is caused by increased vasomotor discharge. But the effects are far from uniform, the argument is one more of analogy than proof and it neglects the possibility that all that may have been done was to remove a normally functioning mechanism from the group of the normal and abnormal mechanisms which combine to maintain arterial pressure.

Among the vasomotor afferents, the sino-aortic buffer system is of much more interest now than it was when experimental chronic neurogenic hypertension was produced in animals by its resection. At that time, lack of interest was conditioned by the facts that (a) hypertensive patients apparently respond normally to pressure over the carotid sinus and (b) the technic of eliciting experimental neurogenic hypertension was uncertain and the mortality sometimes excessive, while (c) the hypertension was attributed principally to an increased cardiac output, which at once differentiates it from clinical essential hypertension. But it must be recognized that carotid pressure is not an adequate test of the delicately balanced function of the sino-aortic receptors and as far as the experimental disease is concerned, the cardiac factor is apparently less significant than the increase in peripheral resistance. The fact that total sympathectomy reduces the blood pressure of these animals to normal indicates that the pressure was sustained by increased vasomotor discharge. Another indication of this is the resistance of these animals to blockade of the sympathetic ganglia by TEAC.[6] This resistance may be attributed to excessive liberation of acetylcholine in the ganglia consequent to the unchecked discharge of the vasomotor center; whatever its cause, the phenomenon demonstrates that abnormal activity of the sino-aortic system is reflected in abnormalities of ganglionic function.

Clinically, estimates of ganglionic resistance to TEAC blockade may serve as a means of selecting patients whose hypertension is associated with excessive vasomotor discharge. Preliminary observations indicate that increased resistance is demonstrable in a minority of patients with essential hypertension. Further study may confirm the assumption that this finding earmarks the hypertension as one predominantly neurogenic, which should, therefore, respond favorably and uniformly to adequate surgical sympathectomy.

But the sino-aortic is by no means the only afferent pathway which may participate in abnormal vasomotor regulation. Another, which arises in receptors principally in the myocardium and also in the lung, is the von Bezold reflex system. Stimulation of this system accounts in some measure for the decrease in arterial pressure and peripheral resistance which characterizes the action of veratrum alkaloids and, parenthetically, may participate in the prolonged decreases of arterial pressure which sometimes follow myocardial infarction. There is some evidence to suggest that afferents which pass through posterior root ganglia have obscure but powerful central vasomotor influence. Intracranial receptors which respond to vasoactive agents in the sense of correcting or opposing their normal peripheral vascular actions have recently been described.[7] These and the extramedullary centers of vasomotor regulation are all but unexplored. The probable rewards from the advanced study of these mechanisms are indicated by the acknowledged influences of the psyche on arterial pressure and on the course of hypertensive disease. Indeed, the phenomenon of the "hypertensive diencephalic syndrome" is a cogent experiment on Nature's part which seems directly to relate abnormal central nervous function to one form of essential hypertension.

Lastly, vasomotor control of arterial pressure must be thought of not only in terms of stimuli which directly change the caliber of the vessels, but also in terms of changes in the capacity of the vessel to respond to standard stimuli and of the effect of nervous influences on vascular reactivity. A familiar example of such a mechanism is the hypersensitivity of vessels which have been deprived of their innervation.[8] Less familiar is the increase in reactivity which follows functional ganglionic blockade, surgical ganglionectomy and section of the spinal cord. Clinically, the latter hyper-

sensitivity is reflected in the paroxysms of hypertension sometimes seen in paraplegias and attributed to release of adrenal medullary secretion. The reverse phenomenon, refractoriness instead of hyperreactivity, is seen in animals exposed to high carbon dioxide concentrations; their vessels become refractory to normal stimuli, not because of paralysis or anesthesia, but because impulses are abnormally transmitted from the sympathetic ganglia; sympathectomy or ganglionic blockade restores this lost vascular reactivity.[9] Thus the normal influence of vasomotor nerves on vascular reactivity is in part one of moderating their response to stimulation. An excess of this influence results in refractoriness and deprivation of it in hyperresponsiveness.

In summary, closer analysis of the participation of the nervous system in the control of arterial pressure and peripheral resistance provides pathways of fertile study. This should be concerned not only with the activity of the efferent vasomotor system in essential hypertension, but, possibly with greater prospect of reward, in an unravelling of afferent pathways and their receptor mechanisms and of the influence and controls of the vasomotor centers.

Unfortunately, neurophysiologic research as it was practiced by such pioneers as Sherrington and Bayliss is almost in abeyance. The von Eulers, Heymans, Liljestrands and Folkows, and those like them who now return to these methods and supplement them with modern methodology, will certainly resolve some part of the riddle of neurovascular function in essential hypertension.

(B) Humoral Mechanisms

The humoral factors which may contribute to the genesis or participate in the maintenance of essential hypertension can be grouped as (1) endocrine, (2) renal, (3) hepatic, and (4) cerebral.

1. Endocrine. Vasomotor adrenergic factors were noted above; the endocrine adrenergic function of the adrenal medulla seems to be limited to the participation of pheochromocytoma in the genesis of hypertensive disease. Exclusion of hyperadrenalemia as a mechanism in essential hypertension suggests that there is little to be gained from further probing into adrenal medullary function in this disease. However, the stable hypertension which sometimes occurs while these tumors are in function and persists after their removal has not yet been adequately explained and remains as a provocative field of further study.

The adrenal cortex is the object of much more present concern than the medulla.[10] Desoxycorticosterone elicits in rats maintained on a high sodium diet both hypertension and hypertensive vascular disease. It is relatively, if not entirely, ineffective in this respect in dogs, but can provoke hypertension in some human beings, particularly those with pre-existing renal damage or loss of adrenal cortical function. It may not be a natural hormone of the adrenal cortex, but it is probable that the natural hormone functions in electrolyte metabolism in the same manner as does desoxycorticosterone. Consequently, experimental desoxycorticosterone hypertension is more than a pharmacologic tour de force. Indeed, Cushing's syndrome is an experiment by Nature which proves the participation of the adrenal cortex in hypertension and nephrosclerosis.

The participation of the adrenal cortex as a *genetic* rather than merely sustaining mechanism of essential hypertension is quite unsolved. The fact that some patients respond to sodium restriction by a decrease of arterial pressure and amelioration of their disease has some analogy to what obtains in the desoxycorticosterone-treated rat. But their defect may be in the response of their tissues to a normal complement of hormone and/or electrolyte rather than to an excess of either substance. Indeed, the mechanism by which sodium excess or an increase in the sodium-potassium ratio of blood or tissues increases arterial pressure has not been analyzed. As concerns hypercorticoidism as a mechanism of essential hypertension, it can only be said that there are no substantial evidences of it, even in the sodium-responsive patients. This is negative evidence and is based on methods which are admittedly crude. Some hypertensive patients do show abnormalities in the ratio of "free" (pH 1 extractable) to bound (glucuronide) corticoid in urine; more elaborate methods have demon-

strated abnormalities in the pattern of 17-ketosteroid excretion in a few patients.

The weight of evidence points away from hypercorticoidism and towards the possibility of a defect in tissue response. Recent preliminary evidence raises the possibility that one determinant of an abnormal response to the hormones of the adrenal cortex is growth hormone, which also elicits hypertension in rats. Clearly, the favorable responses of some few patients to total or subtotal adrenalectomy does not resolve the question. Rather the field is one in which speculation must soon be replaced by fact.

2. Renal. Mechanisms of renal hypertension are still very imperfectly understood. The most obvious is the renal pressor system; this consists of the enzyme renin, which acts on renin-substrate to release angiotonin; angiotonin is then disposed of by blood and tissue angiotonases. The assumption, once freely expressed, was that some abnormality of renal blood flow causes renin to be released and angiotonin to be formed in excess. However, the presence of excessive amounts of either substance in the blood of hypertensive patients or animals has not been proved by any direct means and most have come to the conclusion that, with the methods at hand, these substances cannot be shown to be regularly present in amounts which increase arterial pressure. Further, renal extracts containing renin have been slowly infused in animals and have not caused persistent hypertension; renal hypertension has persisted in animals made unresponsive to exogenous renin. These and other arguments have been advanced against the participation of the renal pressor system in renal hypertension. However, quite recently, prolonged hypertension has been obtained by the continuous infusion of renin in amounts so small that they would not have been found in blood by methods in current use, so that the question is still open.

Further, renin and angiotonin have other than pressor effects, since they induce diuresis, natriuresis and proteinuria. Renin-containing renal extracts in rats cause enlargement of the zona glomerulosa of the adrenal cortex, which is the presumed source of "mineralocorticoid" with the activity of desoxycorticosterone and the same occurs in experimental renal hypertension. The subcutaneous injection of these renin-rich extracts in desoxycorticosterone-hypertensive rats elicits a condition which symptomatically resembles eclampsia, although its renal lesions resemble a violent malignant nephrosclerosis.[11] Thus, there is some association of renal and adrenal mechanisms in experimental hypertension which remains to be studied in more detail. Other mechanisms may also participate. Thus, immunization of animals with renal extracts containing renin prevents the subsequent production of renal hypertension, some of the antisera thus obtained are depressors in animals with renal hypertension, and some of the extracts immunize also against vascular lesions.[12] Again, changes in vasomotor regulation, such as those which follow section of the sino-aortic buffer nerves, considerably alter and enhance responsiveness to renin and angiotonin.

Thus, participation of the renal pressor system in experimental renal hypertension is not proved, but remains as a reasonable hypothesis, although the action is possibly more complex than had been envisioned.[13] The recent almost complete purification of renin points to the probability of a resolution of this problem.

The fact that renal hypertension occurs clinically and that it is humorally mediated stands uncontested, and it is a reasonable assumption that the progress of renal arteriolar sclerosis in essential hypertension adds the renal to the other mechanisms of this disease. The search for mediators of renal hypertension other than the renal pressor system has yielded the concept of the VEM-VDM system, in which vasoexcitor material (VEM) is a substance, not yet identified, but formed under appropriate conditions in the kidney.[14] VEM sensitizes the metarterioles (precapillary arterioles) to the action of adrenaline. Vasodepressor material (VDM), identified as ferritin, inhibits this action. Possibly closely related to VEM is pherentasin, an incompletely characterized pressor substance found in the blood of some patients with hypertension. Another substance of renal origin, the sustained pressor principle, has also been described and seems to be distinct from renin. Thus the humoral mechanism of renal

hypertension is not identified and may be multiple, although to us the renal pressor system is the favored contender. The need for better understanding of these mechanisms and of their better integration with renal, adrenal and vasomotor influences is obvious.

3. Hepatic. Hepatic factors which may participate in hypertension are even more poorly defined than the renal. One substance, VDM, has been identified with ferritin or apoferritin. Renin-substrate is a globulin the hepatic formation of which seems in part to be conditioned by adrenal mineralocorticoid activity. Neither VDM nor renin-substrate seem likely as primary factors in the genesis of hypertensive disease. But there may be hepatic factors or functions which relate more directly to this condition. Thus, it is known that hepatectomized animals lose their vascular reactivity and succumb in circulatory collapse.[15] The mechanism of this profound impairment of vascular reactivity is unexplained; the factors which underlie it may possibly bear on the problems of essential hypertension. But the field has yet to be explored.

4. Cerebral. The brain, in common with other nervous tissue, contains the adrenergic compounds, adrenaline and noradrenaline. The relation of this adrenergic content to "encephalin," a pressor substance present in extracts of cerebral tissue, has not been established, nor has the place of encephalin in cerebral or vascular function.[16] Pitressin might be considered as having a place among cerebral pressor substances. However, it is very doubtful that it functions physiologically as anything more than an antidiuretic factor. The maximum release rate from the gland in man is of the order of 1 milliunit per minute, an amount which would not be pressor.

Quite recently a humorally transmitted vasoactive substance has been found to be released from within the cranium during stimulation of the central end of the cut vagus nerve.[17] This material is not pitressin, nor is it adrenergic. Its demonstration suggests that the central nervous sytem may act as an endocrine organ in the control of arterial pressure. Since both substances are unidentified, the relationship of this cerebral pressor agent to another pressor substance found in ventricular fluid cannot be evaluated. Elucidation of this problem of humoral agents of cerebral origin is an attractive and, in view of the psychic associations of essential hypertension, a tempting field of study.

In summary, the humoral mechanisms which bear on the problem of hypertension show a significant interrelationship between humoral and neural factors and among the humoral agents themselves.[18] Their study not only places great demands upon the chemists, but their interrelationships demand an extraordinary teamwork between chemists, physiologists and pharmacologists. Lastly, no note has been taken in this survey of the participation of depressor substances in the equilibria of humoral agents which determine normotension in healthy subjects, although the possibility exists that hypertension results at times from a lack of the right depressor.

Conclusions

Knowledge of arterial hypertension has advanced rapidly during the past 20 years, so rapidly in fact that much current knowledge is only with great difficulty assimilated into a comprehensive schema. As happens so commonly, the problem has proved more difficult than was anticipated when the research began. Some of this difficulty and disappointment arise from the concept that essential hypertension has a unitary cause or a single mechanism. It is now apparent that progress will be made more rapidly and objectively by a recognition of the problem as one with many facets, in which neural and humoral factors can never operate alone, but only by the displacement of an equilibrium in which many mechanisms participate.

The urgent problem is the separation of essential hypertension as it occurs in patients into etiologic subgroups by objective means, so that appropriate, rational and effective treatment can be instituted. We see now through a glass darkly, but much less darkly and with much more hope than we did a few years ago.

Finally, the problem of essential hypertension is indissolubly mixed with that of hypertensive vascular disease. Progress in the solution of the one will have important connotations

in the approach to the other. The resolution of both will lead to solution of the problem of perfusion of the tissues.

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* This very inadequate list of references is designed merely as an initial aid for those unacquainted with the field.

ABSTRACTS

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BACTERIAL ENDOCARDITIS

Slater, J. L.: A Recurrence of Subacute Bacterial Endocarditis Complicated by Pregnancy. Permanente Found. M. Bull. **9:** 149 (Oct.), 1951.

A case report of subacute bacterial endocarditis in pregnancy is presented. Treatment with penicillin gives pregnant patients a much brighter prognosis than before antibiotic therapy. However, these cases need careful evaluation and constant care throughout their antepartum and postpartum course. Interruption of pregnancy is still influenced both by the cardiac status of the patient and by the stage to which the pregnancy has advanced. The termination of a pregnancy after the twentieth week is a dangerous procedure in all patients with cardiac disease.

When at term, surgical interference, except for purely obstetric reasons, should be avoided. All patients who have valve defects, as well as those who have had subacute bacterial endocarditis, should receive routine penicillin prophylactically before and after delivery. The use of anticoagulants is unnecessary and dangerous. A past history of subacute bacterial endocarditis is not necessarily a contraindication to pregnancy. However, the ultimate fate of patients cured of this disease is as yet unknown.

BERNSTEIN

Lillehei, C. W., Shaffer, J. M., Spink, W. W., Bobb, J. R. R., Wargo, J. D., and Visscher, M. B.: Role of Cardiovascular Stress in the Pathogenesis of Endocarditis and Glomerulonephritis: Observations Including Method of Experimental Production Utilizing Arteriovenous Fistulas. Arch. Surg. **63:** 421 (Oct.), 1951.

Utilizing the fact that dogs with large arteriovenous fistulas may develop spontaneously acquired endocarditis and even acute proliferative glomerulonephritis, the authors developed a method for consistently producing these conditions. Bilateral arteriovenous fistulas were produced in the lower extremities and small doses of bacteria were injected intravenously.

In all five of the dogs subjected to the procedure vegetations were found on the mitral valve leaflets. In addition, the aortic and tricuspid valves were each involved in three of the five animals. Diffuse proliferative glomerulonephritis occurred in two cases.

ABRAMSON

Reismann, G.: The Significance of Serum Lability Tests in the Differential Diagnosis of Endocarditis Lenta. Ärztl. Wchnschr. **6:** 941 (Oct.), 1951.

The author compared the results of various serum lability tests in 50 cases of subacute bacterial endocarditis and in 20 cases of rheumatic endocarditis (endocarditis simplex). The study included the Takata-Ara reaction, Weltmann's coagulation test, the Formol-gel test and the Thymol turbidity test, of which the latter proved to be most valuable. It was positive in the majority of cases with subacute bacterial endocarditis, corresponding, in the Pulfrich photometer, to average values of 17.2 D per cent. It was negative, with one exception, in cases of rheumatic endocarditis (average photometric values 42.2 D per cent). In the former group the reaction became negative with clinical improvement of the condition

PICK

BLOOD COAGULATION

Stirling, M., and Hunter, R. B.: Pharmacology of Bis 3-3'-(4 Oxycoumarinyl) Ethyl Acetate (Tromexan). Lancet **2:** 611 (Oct. 6), 1951.

The pharmacologic action of Tromexan in human subjects was compared with that of dicumarol. It was found that the former drug had certain advantages over dicumarol, namely that it induced hypoprothrombinemia more quickly and that its more rapid destruction allowed day-to-day adjustment of the prothrombin level by altering the oral dosage. However, as in the case of dicumarol, the amount necessary to induce and maintain the desired level of prothrombin activity varied for each individual, and hence repeated prothrombin estimations were still essential.

In 111 cases, the incidence of further thromboembolic phenomena was 4.5 per cent, this satisfactory result being achieved by keeping the prothrombin level below 20 per cent. Still, approximately 19 per cent of cases of pulmonary embolism had a further embolism while under treatment. It was therefore felt that Tromexan should be used prophylactically while heparin was the drug of choice in established thrombosis or embolism.

Water-soluble naphthoquinone derivatives given by mouth were found to counteract Tromexan hypoprothrombinemia in some cases and not in others.

ABRAMSON

CONGENITAL ANOMALIES

Laki, K.: The Action of Thrombin on Fibrinogen. Science **114:** 435 (Oct. 26), 1951.

The author investigated the theory that the role of thrombin, in the clotting mechanism, is to act probably as a hydrolytic enzyme, causing some alteration on the fibrinogen molecule. It was his purpose to determine whether in the process of coagulation, thrombin splits off a peptide bond, freeing a small molecule from the fibrinogen and leaving a slightly altered fibrinogen molecule.

Iodinated fibrinogen was clotted with a small amount of thrombin, forming a firm gel. This was then liquefied by heating and the protein was removed with a concentrated Ringer solution. The supernatant was found to stimulate the frog's heart, the potent factor being considered to be a peptide. The problem of whether this substance was really split from fibrinogen by thrombin was left for future study.

ABRAMSON

Wenger, R., and Wick,. E: The Esophagus Electrocardiogram in Congenital Anomalies of the Heart and Great Vessels. Arch. Kreislaufforsch. **17:** 246 (Oct.), 1951.

The authors studied 41 cases with various congenital cardiovascular anomalies using esophageal leads. In 10 cases of Fallot's tetralogy, the ventricular complex in low esophageal leads was QR six times, RS two times, and in the rest a QR or a W-shaped complex The ventricular complex was completely inverted (QS) at ventricular levels in two cases of isolated pulmonary stenosis, who occasionally showed marked right axis deviation in the standard leads (Eisenmenger's complex, situs inversus). At autopsy, excessive right ventricular hypertrophy was evident. A case of tricuspid atresia, with left axis shift in the standard leads, showed an upright complex in the deep esophagogram. In seven cases with atrial septal defect, two of which were associated with pulmonic stenosis, right bundle branch block was present in the conventional leads and a W-shaped complex in the esophageal leads. Normal QRS complexes were seen in cases with ventricular septal defect, coarctation of the aorta, and idiopathic dilatation of the pulmonary artery. The authors believe that the use of esophageal leads may be helpful in the diagnosis of congenital anomalies of the heart.

PICK

Gross, R. E.: Treatment of Certain Aortic Coarctations of Homologous Grafts: a Report of Nineteen Cases. Ann. Surg. **134:** 753 (Oct.), 1951.

Nineteen patients with coarctation of the aorta were treated by removal of the abnormal portion of the vessel and by insertion of an arterial homograft. In each instance it was impossible to deal with the lesion by the usual procedure of excision and primary anastomosis.

The graft employed was generally obtained from fresh autopsy or medical-examiner material, being preserved in a modified Tyrode's solution which contained 10 per cent human serum and 1 per cent glucose. The segments of vessels were stored at a temperature of 2 to 4 C.

Two deaths were precipitated by postoperative renal shutdown, uremia, and hyperkalemia. The remaining 17 cases were followed for from several months to three years and in no instance was rupture or aneurysm formation noted. In 14 patients the results were excellent, the blood pressure in the arms being restored to normal.

ABRAMSON

Muller, W. H., Jr.: The Surgical Treatment of Transposition of the Pulmonary Veins. Ann. Surg. **134:** 683 (Oct.), 1951.

The author presented two cases of complete transposition of the pulmonary veins. Cardiac catheterization was of value in the diagnosis. Passage of the catheter into the right lung field from either the superior vena cava or right auricle was considered to be good evidence for the presence of transposition of pulmonary veins. If the catheter was found in the left lung field, this did not necessarily confirm

the diagnosis, because of the possibility that it may have passed through a patent foramen ovale into a normal left pulmonary vein. Approximately the same oxygen content of the blood was found in the right auricle, right ventricle and a peripheral artery.

Both cases were treated surgically by anastomosing the end of the left auricular appendage and the side of a large superior pulmonary vein. One patient had an uneventful postoperative course and later demonstrated an increased exercise tolerance. Although previous to operation cyanosis was present, this was no longer noted postoperatively. The second patient died about 10 hours after completion of the operation.

It was the belief of the author that this type of operation might reduce the venous return and pressure in the right auricle, increase the venous return to the left auricle and thus cause the patent foramen ovale to become smaller.

ABRAMSON

CONGESTIVE HEART FAILURE

Lasché, E., Perloff, W. H., and Durant, T. M.: Some Aspects of Adrenocortical Function in Cardiac Decompensation. Am. J. M. Sc. **222:** 459 (Oct.), 1951.

Evaluation of the adrenocortical function of 23 patients with various degrees of congestive heart failure was made. A wide variety of etiologies were responsible for the cardiac disease, but no attempt was made to assay the effects of these specific etiologies upon the adrenal directly. It is therefore assumed that any alteration in adrenal function must be due to congestive failure. Insulin tolerance tests were employed as the stressful stimulus promoting adrenal cortex activation. Blood glucose and eosinophil responses were followed after insulin administration. Two patients were given ACTH for a week. Urine volumes and the 24 hour excretion rates of 17-ketosteroid and corticoids were determined.

In patients with congestive failure of recent onset, the rates of steroid hormone excretion may be normal. However, in the majority of cases a significant lowering of the excretion levels was noted. Following insulin administration, hypoglycemic unresponsiveness appeared in patients with decompensation of more than six months' duration while an impaired eosinophil response was noted in those with decompensation for two years or more. ACTH produced a fall in eosinophils in two patients but did not produce striking changes in corticoid excretion rates until after the administration of a mercurial diuretic. The administration of mercurial diuretics raised the excretion rate of 11-oxysteroids tenfold in edematous patients but produced little change in the urinary levels in the nonedematous patients. Diuresis did not increase the urinary 17-ketosteroid excretion.

The evidence presented suggests that there is decreased adrenocortical function in chronic cardiac decompensation, and that there may be retention of the 11-oxysteroids at the renal level in these patients.

SHUMAN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Doak, Edmond K.: Esophageal Hiatus Hernia Simulating Coronary Artery Disease. South. M. J. **44:** 918 (Oct.) 1951.

Patients whose symptoms strongly suggest heart disease should be considered as having heart disease until proved otherwise. In the acute attacks, this proof depends upon and must wait upon the exclusion of myocardial injury. Should positive evidence of myocardial infarction be equivocal or lacking, roentgen search for hiatus hernia is in order. Some physicians might feel impelled to begin anticoagulant therapy before positive objective evidence of infarction is obtained. In this connection, one might well remember the frequency of esophageal hiatus hernia and its propensity to bleed.

All cases of angina pectoris may properly be examined for hiatus herniation and should a hernia be found, the coronary circulation should be evaluated by the Master test or the Levy test. Even in the presence of proved angina pectoris proper management of an existing hiatus hernia may ameliorate the distressing symptoms.

BERNSTEIN

Morrison, L. M.: Reduction of Mortality Rate in Coronary Atherosclerosis by a Low Cholesterol-Low Fat Diet. Am. Heart J. **42:** 538 (Oct.) 1951.

The author studied over a three year period the effects of a low cholesterol-low fat diet on the morbidity and mortality rates of 100 patients with recent proved coronary thrombosis and myocardial infarction. Patients were taken in alternate order, one patient being placed on the usual prethrombosis diet (estimated to contain 80 to 160 Gm. of fat, 200 to 1800 mg. cholesterol) and the next alternate patient being placed on the test diet (1500 calories, 20 to 25 Gm. of fat, 50 to 70 mg. cholesterol). The age and sex distribution was the same in both groups. Supplementary vitamins were taken by the latter group.

In the dietetically treated group the men lost 19 pounds of weight, and the women 17 pounds. The weights of the control series were not significantly altered. At the end of three years, 43 of the 50 patients on the low fat-low cholesterol diet were living, whereas 35 of the 50 patients on their "normal" or prethrombosis diet survived. An appreciable number of patients required from one to two years on the low fat dietary regime before a fall in serum cholesterol was manifested. The total serum lipids

tended to decrease before the serum cholesterol levels. The subjective symptomatic improvements of the dietetically treated patients consisted of an increase in well-being, increase in capacity for work, and increase in morale or optimism. The author notes that this may be due in part to the factors of weight reduction and psychotherapy.

Although the mortality in the dietetically treated patients was reduced, the author says statisticians felt his data were not amenable to statistical analysis. Further controlled studies are suggested. A dietary program and a sample menu are appended.

HELLERSTEIN

Miller, M., and Bernstein, E. T.: Coronary Insufficiency Following Penicillin Treatment of Cardiovascular Syphilis. Exper. Med. & Surg. **9:** 381 (May, Aug., Nov.), 1951.

The authors record a case with clinical and electrocardiographic evidence of acute coronary insufficiency following the injection of procaine penicillin (600,000 units) in a 48 year old colored female with uncomplicated syphilitic aortitis. The patient complained of rather marked precordial pressure not related to effort. The electrocardiogram changed from a normal one seven days previously to one with T isoelectric; T wave in leads II, III, V_5 and V_6 became inverted and T in V_4 was diphasic. The authors concluded that this is a Jarisch-Herxheimer reaction, or therapeutic shock, following penicillin, taking the form of a coronary insufficiency.

The penicillin injections were continued without recurrence of the precordial pressure, and an electrocardiogram taken within five weeks was normal again.

RINZLER

ELECTROCARDIOGRAPHY

Cuttino, John T.: Contrast between the Anoxia of Experimental Pulmonary Arterial Occlusion and of the Tracheal Obstruction with Special Reference to Changes in the S-T Segment and T Wave. South. M. J. **44:** 909 (Oct.), 1951.

Study of continuous electrocardiographic tracings of dogs dying of anoxia, as a result of ligation of the main pulmonary artery, consistently showed depression of the S-T segment and inversion of the T wave within 6 to 10 seconds, followed by restoration of their normal configuration within from 40 to 150 seconds, and by significant increase in amplitude of the T wave. By contrast, dogs dying of anoxia due to tracheal obstruction failed to show the depression of the S-T segment and inversion of the T wave but showed comparable increase in amplitude of the T wave.

The evidence from these experiments tends to support the theory that anoxia of the myocardium is the chief factor in the causation of death in massive pulmonary embolism.

BERNSTEIN

Lasser, R. P., Borun, E. R., and Grishman, A.: Spatial Vectorcardiography: Right Ventricular Hypertrophy as Seen in Congenital Heart Disease. VII. Am. Heart J. **42:** 370 (Sept.), 1951.

The authors have studied the vectorcardiograms of right ventricular hypertrophy in 25 patients with congenital heart disease, eight cases of tetralogy of Fallot, eight with uncomplicated pulmonary stenosis, pulmonary hypertension with interatrial septal defect in two, and Eisenmenger's complex in one. A modification of the Duchosal-Sulzer system of lead placement was employed, and simultaneous horizontal, frontal and sagittal vector loops recorded. The vectorcardiograms were divided into three groups on the basis of similarity of vector patterns.

In the first group the vector loops pursue the following course: after leaving the isoelectric center spot, they travel to the right, upward, and anteriorly for a short time. A sharp turn is made and the pathway proceeds to the left, downward, and slightly posteriorly. A 170 degree clockwise turn is then made and the centripetal limb returns to isoelectricity by running to the right upward and anterior to the centrifugal limb. In the second group, the right ventricular hypertrophy and hypertension were more marked. The spatial loop differs from the first group by being oriented to a further right anterior position, the segment of vector pathway which extends to the left and downward becomes much shorter, and the returning or centripetal limb assumes a more anterior position. In the third group, there was left axis deviation, in the presence of marked right ventricular hypertrophy. The horizontal loop is predominantly posterior, with the vector loop oriented toward the right posterior octant. The characteristic features of the QRS $_{SE}$ loops found in patients with hypertrophy of the right ventricle makes it possible to distinguish these from the vectorcardiograms obtained in patients with markedly vertical electrical position or atypical right bundle branch block.

The authors emphasize the close correlation of form and timing of the precordial electrocardiogram and vectorcardiogram. Since the chest lead pattern of the precordial area could be predicted from a vectorcardiogram whose component leads were at the patient's lumbar area, the precordial leads appear to act as distant electrodes.

HELLERSTEIN

Simonson, E., and Berman, R.: Differentiation between Paroxysmal Auricular Tachycardia with Partial A-V Block and Auricular Flutter. Am. Heart J. **42:** 387 (Sept.), 1951.

The differentiation between paroxysmal auricular tachycardia and auricular flutter is difficult when partial A-V block is associated with the former. The most important widely accepted criterion is the contour of the P-P or T-P intervals. In auricular tachycardia, these intervals are briefly isoelectric, while in flutter most leads show continuous motion of the galvanometer (Lewis). In addition the auricular rate is usually higher in flutter than in paroxysmal tachycardia. In 10 patients with auricular tachycardia and partial A-V block the authors were unable to differentiate between flutter and tachycardia on the basis of the appearance of isoelectric P-P or T-P intervals, the auricular rate, or response to carotid sinus pressure.

These results are considered compatible with the experiments of Scherf, Prinzmetal and associates which showed that the basic mechanism of flutter and auricular tachycardia is a single ectopic focus, with a faster rate of auricular contraction in the former. The chief clinical difference between ordinary paroxysmal auricular tachycardia, a relatively benign condition usually not associated with heart failure, and auricular tachycardia with A-V block was the presence of heart failure in 9 of the 10 patients studied.

HELLERSTEIN

Baer, L. J.: Electrocardiographic Effects of Emetine Hydrochloride. Mil. Surgeon **109:** 120 (Oct.) 1951.

The depression or inversion of T waves in the electrocardiogram is the most common ECG toxic manifestation of emetine in man. Within the dose range of 65 mg. per day for 9 to 10 days the exact changes in the myocardium which occurred to produce T-wave changes are not known. However, the T-wave changes are reversible within this dose range, the ECG returning to normal within 3 to 57 days in this series. Other than T-wave alterations, electrocardiographic changes associated with emetine administration are infrequent. Such changes appeared in 1.4 per cent of the cases in this series. Auricular fibrillation, premature auricular systoles, P-wave changes, abnormal QRS, shifting pacemaker, and nodal rhythm have all been reported as occurring rarely during emetine therapy.

From the evidence it seems clear that there must be susceptibility before a patient will show toxic manifestations of emetine within the dose range of 65 mg. per day for 9 to 10 days. Other toxic manifestations besides the ECG changes have a tendency to occur early in the course of emetine and may disappear during emetine therapy. In contrast the ECG changes are progressive. The use of the electrocardiogram is, therefore, the best method for finding the patient who is susceptible to emetine.

BERNSTEIN

Broustet, P., Capsec-Laporterie, J., and Gazeau, J.: Severe Forms of the Syndrome of Wolff-Parkinson-White. Arch. Mal. Coeur **44:** 901 (Oct.), 1951.

The authors report a case of W-P-W syndrome in a 31 year old man who in the absence of a history or clinical findings pointing to organic heart disease developed attacks of protracted and untreatable paroxysmal tachycardia. Frequent electrocardiograms recorded during the attacks revealed various patterns. In some of them the ventricular complexes were normal in contour, in contrast to the typical W-P-W pattern seen during sinus rhythm. In other attacks, there was an auricular tachycardia of 250 per minute, associated with a regular ventricular rate of 125. The QRS was widened and similar to, but not identical with, the QRS observed during pre-excitation. On some occasion this type of QRS appeared at the rate of the rapid auricular action (250). Therapeutic attempts to stop the tachycardia, including vagal stimulation by carotid sinus pressure, I.V. acetylcholine, as well as quinidine and digitalis, remained without effect. Once, the tachycardia was reverted to sinus rhythm with W-P-W complexes by administration of $\frac{1}{8}$ mg. of atropine.

The author feels that observations of tachycardias with apparently multifocal origin in cases of W-P-W syndrome, supports the concept that hyperexcitability of the myocardium rather than an anomalous atrioventricular pathway of conduction is responsible for the electrocardiographic pattern of pre-excitation.

PICK

Wille, Th.: Contribution to the Pathogenesis of the W-P-W Syndromes with Special Reference to the Vegetative Nervous System. Ärztl. Wchnschr. **6:** 946 (Oct.), 1951.

The author reports eight cases of Wolff-Parkinson-White syndrome who showed frequent variations of the electrocardiographic pattern of normal and abnormal conduction. All cases had signs of neurovegetative disturbance, but no clinical evidence of heart disease. In three instances W-P-W complexes could be observed regularly in electrocardiograms taken in the early morning hours. In one of them the anomalous pattern could be elicited repeatedly by subcutaneous injection of adrenaline. Other pharmacologic tests (Hydrergine, atropine and Prostigmin) performed in this and in the other two cases were without effect on the electrocardiogram.

On the basis of his observations the author believes that in cases revealing a W-P-W pattern of intermittent type, the anomalous ventricular activation is due to functional impairment of the conduction system, either by "Anlage" or acquired following myocarditis. In cases with neurovegetative lability the specific system of the myocardium may represent a "locus minoris resistentiae" for

various endogenous and extraneous impulses, manifested in the electrocardiogram in form of the W-P-W syndrome.

PICK

Frau, G.: The Pathogenesis of Disturbances of Ventricular Conduction. An Experimental Contribution. Cardiologia **19:** 2 (fasc. 1), 1951.

The author produced transient intraventricular block in dogs by injection of a small amount of a 1 per cent solution of quinine bichloride into the ventricular septum or into the free wall of the ventricles. Direct electrocardiograms were obtained by a multibeam cathode oscillograph, recording simultaneously from nine different points of the epicardium.

A typical pattern of bundle branch block was seen only when quinine infiltrated the intraventricular septum. The appearance of a right or left conduction disturbance corresponded to the side of injection. Injection of the quinine solution into the free myocardium of either ventricle never disturbed the normal over-all sequence of ventricular activation, regardless of the area involved, and produced only insignificant alterations of the electrocardiographic pattern, indicating a local disturbance of conduction.

On the basis of these experiments, the author divides disturbances of ventricular conduction into two categories. The first, termed *intra*ventricular, has its origin in the contractile myocardium where the delay of conduction is restricted to a small area. Such cases resemble "focal block" as described by Katz. In contrast to it, a second type, named by the author "*inter*ventricular delay of conduction," results from a primary alteration of the bundle branches, influences the activation of the whole affected ventricle and, thus, invariably produces a modification of activation of the entire ventricular myocardium. This applies to several clinical varieties with well-defined electrocardiographic characteristics, which, according to the author, can be classified in the order of the degree of conduction delay: simple deviation of AQRS, ventricular hypertrophy or strain, partial bundle branch block, complete bundle branch block, and, finally, bilateral bundle branch block.

PICK

Milnor, W. R., Genecin, A., Talbot, S. A., and Newman, E. V.: A Vectorcardiographic Study of the Q_3 Deflection in Cases of Myocardial Infarction and in Normal Subjects. Bull. Johns Hopkins Hosp. **89:** 281 (Oct.), 1951.

The authors attempted to determine whether the spatial vectorcardiogram would help distinguish the "Q_3" deflection in normal subjects from that due to infarction of the posterior-inferior wall of the left ventricle. Spatial vectorcardiograms were done on 53 persons who showed a Q wave in lead III of the electrocardiogram. Twenty-two were patients with a history of myocardial infarction and 31 were normal subjects.

The vectorcardiograms were recorded from leads based on the Wilson "tetrahedron" using lead I for the horizontal, lead VF for the vertical, and VB for the anteroposterior axis of the spatial reference system. As the Q_3 on the electrocardiogram corresponds to the earliest portion of the QRS loop, the earliest portion of the QRS loop travels from the nullpoint (analagous to isoelectric line on the ECG) in almost all vectorcardiograms in a fairly straight line for at least 0.012 second. This the authors call the "initial QRS vector."

In the frontal projection there was no consistent difference between the normal and the infarction groups. There were no distinguishing features found in the standard or unipolar extremity leads, which also lie in the frontal plane. However, in the sagittal projection it was found that the initial QRS vector of the normal group was between plus 5 degrees and minus 62 degrees, whereas in the group with infarction it fell between minus 68 degrees and minus 97 degrees.

This is apparently in accord with the electrocardiographic theory that the Q waves in an electrocardiogram, when considered as vectors, point away from the area of myocardial infarction. The infarcted area in cases having a Q_3 is usually in the postero-inferior wall of the ventricles, hence the almost vertical direction of initial QRS vector.

MARGOLIES

Duchosal, P. W., and Grosgurin, J.: Alterations of the Order of Ventricular Activation in the Normal Heart. Cardiologia **19:** 59 (Fasc. 1), 1951.

Electrocardiograms and vectorcardiograms of a case with auricular bigeminy are shown from a healthy young man without any clinical evidence of cardiac hypertrophy. The contour of the premature beats varies between the patterns of right and left bundle branch block. Many transitional complexes are seen, some with the typical contour of right and left ventricular hypertrophy.

On the basis of these observations, it is concluded that electrocardiographic patterns of ventricular hypertrophy can be imitated by minor delays of intraventricular conduction. The frequent association of the latter electrocardiogram with actual ventricular hypertrophy is due to slowing of impulse transmission through thickened ventricular myocardium.

PICK

Mahaim, I., and Barrelat, J. A.: Ventricular Tachycardia with Retrograde Conduction and Reversed Wenckebach Periods. Cardiologia **19:** 62 (Fasc. 1), 1951.

The authors present electrocardiograms of two cases taken during paroxysms of ventricular tachy-

cardia which showed evidence of ventricular activity of different types. In the first case, regular P waves at a slower rate than that of the ventricles indicated complete A-V dissociation, the auricles being activated by impulses from the sinus node. In the other case, inverted P waves could be identified in leads II and III, occurring at intervals of alterating length, thus indicating retrograde conduction of the rapid ventricular impulses, with second degree V-A block and Wenckebach periods at a regular 3:2 ratio. The author emphasizes the importance of identification of P waves in the differential diagnosis of paroxysmal ventricular tachycardia.

PICK

Gillmann, H.: On the influence of Proximity Potentials, of the Location of the Electrical Zero Point, and of the Limits of the Electrical Field upon "Unipolar" Precordial Leads. Arch. Kreislaufforsch. **17**: 284 (Oct.), 1951.

The authors present schematic diagrams in support of the concept which explains the contour of precordial leads as projections of the spatial vectorcardiogram upon the horizontal plane. Thus, proximity potentials of right or left ventricle are not alone responsible for certain precordial patterns, but may, especially in leads V_2 to V_4, modify theoretic electrocardiographic patterns. Other modifications of these expected patterns may be due to a shift of the theoretic zero point of the vectorloop. This can occur normally with changes of the position of the heart with respect to the fixed precordial positions of the electrodes, or, under abnormal conditions, with changes of the direction of depolarization and repolarization. Finally, irregularities of the potential lines of the electrical field in the human body may have considerable influence on the configuration of the precordial electrocardiogram.

PICK

Myers, G. B., Sears, C. H., and Hiratza, T.: Correlation of Electrocardiographic and Pathologic Findings in Ring-like Subendocardial Infarction of the Left Ventricle. Am. J. M. Sc. **222**: 417 (Oct.), 1951.

The authors discuss the difficulties encountered in the diagnosis of subendocardial infarction, and present electrocardiographic and pathologic studies performed on 15 cases in which this condition was demonstrated. The distribution of the lesions in the majority of cases was found to involve the subendocardial half of the free wall and the left side of the septum. These lesions were diffuse and did not appear to involve individual muscle bundles. Clinically, these patients showed a greater incidence and severity of circulatory collapse than acute localized infarction.

The electrocardiographic findings considered diagnostic of subendocardial infarction of the free wall of the ventricle and septum were (a) Q R complex with initial downstroke of 0.03 second or more from onset to nadir and more than 25 per cent of the succeeding R wave (b) Q R complex with definite notching of the upstroke of the R wave recorded in unipolar leads facing the left ventricle. Variations of these QRS patterns were recorded from widely distributed sites, including esopahgus, stomach and lumbar areas in cases with infarction of the free wall of the ventricle, but not the septum. Incomplete left bundle branch block was found in five cases and was regarded as compatible with but not pathognomonic of septal infarction. Analysis of the RS-T segment and T waves in these cases showed Q T interval prolongation in each. Elevation of the RS-T segment in aV_R, a manifestation of acute subendocardial infarction, was seen in only three cases. Depression of the RS-T junction with sagging of the segment and a disphasic or inverted T wave in the left ventricle leads were findings considered typical of subendocardial injury.

SHUMAN

HYPERTENSION

Perera, G. A.: The Life History of One Hundred Patients with Hypertensive Vascular Disease. Am. Heart J. **42**: 421 (Sept.), 1951.

The author presents data concerning the life history of 100 patients with hypertensive vascular disease followed from the onset of hypertension until death. Hypertensive vascular disease in this series began in early adult life (average age of 32 years) and had an average duration of 19 years which is longer than generally appreciated.

Although 24 women had pregnancies during this period of observation, there was evidence of relationship between pregnancy and the onset of disease in only four. Since hypertension may have preceded conception in two patients in whom the last normotensive readings had been many months before, the author suggests that sustained elevation of blood pressure after a pregnancy indicates antecedent disease.

Multiple complications (cerebral, cardiac, renal, retinal) were more frequent than single, and the time of onset and the intensity of a particular complication varied from patient to patient. In terms of single complications, an average survival of five or more years occurred after all complications except in patients who had sustained cerebral vascular accidents or who have exhibited papilledema or nitrogen retention.

HELLERSTEIN

Chesky, K., Moser, M., Taymor, R. C., Master, A. M., and Pordy, L.: Clinical Evaluation of the Ballistocardiogram. II. Heart Disease—Hypertension, Angina Pectoris, and Myocardial Infarction. Am. Heart J. **42**: 328 (Sept.), 1951.

The authors studied the ballistocardiogram of a series of 135 cases with heart disease using a photocell displacement apparatus, in order to evaluate it empirically as a routine clinical diagnostic method in cardiology. Emphasis was placed on the qualitative appearance of the various component waves of the ballistocardiogram.

In 10 patients with essential hypertension and 40 with hypertensive heart disease, only two had completely normal ballistocardiograms at rest, although 28 had normal electrocardiograms. In 45 patients with normal resting electrocardiograms but positive response to the Master "two-step" test, the ballistocardiograms were abnormal in 34 (75 per cent) at rest, and became abnormal in 19 of 21 patients who were exercised. In 40 patients with previous myocardial infarction, at rest the electrocardiograms were abnormal in 36, and the ballistocardiograms were abnormal in 37.

The most frequent ballistocardiographic alteration encountered in the abnormal cases was very small or absent I waves. This abnormality is not specific for any one particular cardiovascular disease entity. This fact should be borne in mind when one applies the finding of an abnormal ballistocardiogram tracing in a specific clinical case. The authors state that their empirical findings attest to the practical value of the ballistocardiogram, and the unsolved theoretic basis of the technic in no way limits the value of the findings.

HELLERSTEIN

Schroeder, H. A.: The Antihypertensive Influence of Certain Sulfhydryl Compounds. Science **114:** 441 (Oct. 26), 1951.

A number of sulfhydryl compounds were found to have a hypotensive effect on rats made hypertensive by partial constriction of a renal artery. The substances which have this effect contained sulfhydryl groups on the ends of chains of two or three carbon atoms, whereas inactive ones were either cyclic structures with the SH group on a ring or in the middle of a carbon chain. The doses employed were relatively large (5 to 10 mg. per rat) and the duration of normal tension was long. A permanent hypotensive effect was obtained when pyruvic acid was also given.

The action of such pressor amines as norepinephrine and angiotonin was rendered inactive in an animal previously prepared by the intravenous injection of some sulfhydryl substances. All the compounds inhibited by sulfhydryl substance contain either hydroxyl or carbonyl groups. The application of these findings to the study of human hypertension deserves further attention.

WAIFE

Gomez, D. M.: Evaluation of Renal Resistances, with Special Reference to Changes in Essential Hypertension. J. Clin. Investigation **30:** 1143 (Oct.), 1951.

This report is a mathematic treatment of various aspects of renal hemodynamics. After making certain necessary assumptions, equations are derived for the calculation of resistances in various parts of the renal vascular system.

Based on these concepts the resistance in the venular system of 22 normal subjects was found to be a significantly large part of the total renal resistance, and in the average equals the resistance of either the afferent or efferent arterioles.

Data on 51 subjects with essential hypertension show that the afferent arteriolar resistance is significantly increased above normal. The lowest value among hypertensives exceeds the highest normal value. This is the predominant change in the renal circulation in hypertension. The increase was relatively greater than the increase in systemic arteriole resistance. The increase in efferent arteriolar and venular resistance is slight in hypertension and may be in part due to the passive decrease in caliber resulting from the decrease in glomerular and postglomerular pressure.

WAIFE

Marshall, A. G.: Aberrant Renal Arteries and Hypertension. Lancet **261:** 701 (Oct. 20), 1951.

In a series of 400 necropsies, the incidence of aberrant renal arteries was found to agree with previous reports. The incidence of aberrant renal arteries was significantly higher in the hypertensive subjects than in the remainder of the series. In view of the difficulty of defining hypertension, the relation of aberrant arteries to its anatomic features (enlarged heart and hyaline renal arteries) was examined. The same significant correlation was found, though there was a difference of emphasis in the two sexes. The age of the subject was not significant. No correlation was apparent between hypertension and the number or type of such arteries.

No morbid-anatomic explanation could be found for the higher incidence of hypertension in patients with aberrant renal arteries. The authors believe that familial differences in the incidence or distribution of aberrant renal arteries may explain why hypertension is commoner in some families than in others.

BERNSTEIN

Austen, S., and Westphal, K.: The X-Ray Picture of the Sella Turcica in Genuine Hypertension and in Angina Pectoris. Deutsche. med. Wchnschr. **43:** 1329 (Oct.), 1951.

Endocrine stigmata such as small genitalia, sexual disturbances, amenorrhea, abnormal distribution of body hair and fat, which are seen not infrequently in patients with essential hypertension and/or angina pectoris, were studied in 169 cases and correlated with roentgenograms of the skull. Special consideration was given to the size and contour of of the sella turcica. It was found to be abnormal, and,

in the majority, larger than the average normal size in 53 per cent of cases with hypertension, in 60 per cent of cases with angina pectoris, and 38 per cent of cases with myocardial infarction. In view of these observations the authors conclude that endocrine imbalance may contribute to the pathogenesis of the mentioned diseases.

PICK

Aole, V., Dahl, L., Cotzias, G., Dziewiatkowski, D., and Harris, C.: Dietary Treatment of Hypertension. II. Sodium Depletion as Related to Therapeutic Effect. J. Clin. Investigation **30:** 584 (June), 1951.

The effect of wide variations of dietary sodium was studied in five subjects with benign and uncomplicated hypertension. They were kept for five to seven months on a basic diet low in sodium (less than 7 mEq. per day). For the first two to four months they were given supplemental salt tablets at a dosage of 180 mEq. per day, after which time the sodium was reduced to 7 mEq. per day by omission of the tablets. Ten weeks later, the sodium intake was returned to the higher level.

During the period of high sodium intake, blood pressure of all the patients remained elevated. Weight losses and large variations in the intakes of protein and water during this period were without significant effects on the blood pressure. Restriction of dietary sodium to 7 mEq. per day resulted in significant reduction in blood pressure. Changes in the exchangeable sodium as measured by dilution of radiosodium, were studied during the periods of high and of low sodium intake. There was a loss of 14 to 20 per cent of exchangeable sodium during the first month of sodium depletion, which was restored by the readministration of salt. Serum sodium was unaffected by variations in sodium intake.

There was a lag of about one week in the adjustment of the urinary excretion of sodium to changes in dietary sodium. The ratio of sodium to chloride excretion was the same as that found in serum, suggesting that the sodium lost during the early stages of salt depletion derived from a source with the composition of extracellular fluid. Since the loss of water from the body was not proportional to the loss of sodium, it was postulated that the surplus extracellular water shifted into an intracellular position, and thereby increased cellular hydration by about 5 per cent. The reverse situation held during periods of salt administration. It was further postulated that the low sodium diet exerted its beneficial effect in hypertensive patients by causing an increase in cellular hydration.

CORTELL

Lee, R., and Holze, E.: Peripheral Vascular Hemodynamics in the Bulbar Conjunctiva of Subjects with Hypertensive Vascular Disease. J. Clin. Investigation. **30:** 539 (June), 1951.

The bulbar conjunctiva of 45 hypertensive individuals with no evidence of renal or hepatic disease or congestive failure, was examined by means of a slit-lamp microscope. The general state of the capillary bed was noted, and in certain cases, the velocity of blood flow in the metarterioles, capillaries and collecting venules, and the sensitivity of the metarterioles and precapillaries to epinephrine and cold were measured. In addition, similar observations were made on 33 normotensive individuals with a variety of systemic diseases, and 72 normotensive subjects without disease.

Although no absolute correlation between any single feature of the conjunctival vascular system and either the diastolic level of pressure, the severity of symptoms, or the duration of the hypertension could be found, a composite state of the peripheral vascular bed in hypertension evolved that was not observed in patients with other diseases, or in normal subjects. There was metartiolar narrowing, augmented spontaneous vasomotor activity in precapillary sphincters, coiling, looping, and tortuosity of many vessels, a heightened sensitivity of metarterioles and precapillaries to topically applied epinephrine, and a reduced velocity of peripheral blood flow.

Of interest is the fact that a comparable elevation of the vascular reactivity to epinephrine was observed in cases of Laennec's cirrhosis and in patients with hyperglobulinemia without hypertension. Four patients with spontaneous remission of previous hypertension showed the same phenonema found in the conjunctival vascular bed of patients with sustained hypertension.

CORTELL

PATHOLOGIC PHYSIOLOGY

Shepherd, J. T.: Effect of Cigarette-Smoking on Blood Flow through the Hand. Brit. M. J. **4738:** 1007 (Oct.), 1951.

The frequency of inhalation of tobacco smoke has been determined in 50 male subjects. Simultaneous measurements of hand blood flow and stethographic records of the respiratory movements have been made in moderate cigarette-smokers during smoking and imitation smoking. Inhalation of the tobacco smoke at intervals of a minute (approximately the normal rate) leads to a transient decrease in flow at the moment of inhalation. A similar decrease occurs when inhalations of the same depth are carried out with the cigarette unlit. The transient decrease in flow is therefore due to the physiologic effect of the deep breath associated with the inhalation, and not to the pharmacologic action of substances in the tobacco.

Apart from this decrease in flow on inhalation, the general level of hand blood flow is unaltered during and immediately after smoking one cigarette at this rate. When cigarette smoke is inhaled every 20 seconds—that is, more rapidly than normal—the hand blood flow steadily decreases during the smoking period.

When cigarettes are smoked at a rate in excess of the normal the resulting decrease in hand blood flow is therefore mainly pharmacologic and not physiologic in origin.

BERNSTEIN

Bing, R. J., Heimbecker, R., and Falholt, W.: An Estimation of the Residual Volume of Blood in the Right Ventricle of Normal and Diseased Human Hearts in Vivo. Am. Heart J. **42:** 483 (Oct.), 1951.

The authors describe a method for estimating the residual volume of blood in the right ventricle of normal and diseased human hearts. The procedure consists of catheterization of the right ventricle and the pulmonary artery with a double lumen catheter and the injection of Evans Blue into the right ventricle. The dye dilution is determined by withdrawing blood by suction from the pulmonary artery and passing it through a photoelectric dye recorder. The residual volumes are estimated from the slope of the photographically recorded dye dilution curve.

Two artificial circulation models (pulsatile and nonpulsatile) were used to test the accuracy of the method and to establish the relationship between the various factors which influence the downward slope of the dye dilution curve. The slope is determined not only by the rate of flow of blood from the ventricle into the pulmonary artery, and by the dilution of dye by ventricular blood, but also by the length of tubing connecting the pulmonary artery with the cuvette of the photoelectric dye recorder.

The author states that it is not possible to state the accurate relationship between the slope of the dye dilution curve and the ratio of flow to residual volume for the human right ventricle. The average right ventricular residual volume was found to be 50 cc. per square meter. The ratio of residual volume to stroke volume in the normal right ventricle was 1.7. Large residual volumes (350 cc.) were found in patients with right ventricular failure, and the ratio of residual volume to stroke volume was significantly elevated to 13.6. In patients with mitral stenosis and large residual volumes, right heart failure was usually present.

HELLERSTEIN

Kjellberg, S. R., Lonroth, H., Rudhe, U., and Sjostrand, T.: The Relationship between the Heart Volume and the Blood Volume and its Physiological and Pathological Variability. Acta med. scandinav. **140:** 446 (July), 1951.

These investigators calculated the regression of the heart volume (H), determined roentgenologically in the prone position, with respect to the body weight (W) and the blood volume (T), determined as the total amount of hemoglobin in the body in a series of normal men and women, including some athletes. The regression equation obtained was $H = 2.8\ W + 0.5\ T + 140$. The standard deviation from this formula was 8 per cent.

A similar examination was made in a group of patients with suspected or definite heart disease and hypertension. The majority of these patients showed a higher value for the heart volume than that calculated according to the regression formula; in 60 per cent of them the deviation exceeded three times the standard deviation for normals.

The fact that the enlargement of the heart was not parallel to an increase in the volume of the blood is considered to indicate that a pathologic increase in the volume of the heart is a reflection of changes in the distribution of the blood, of the relationship between the diastolic volume and the tension of the myocardial fibers or of the size of the heart muscle mass.

ROSENBAUM

Hegnauer, A. H., Flynn, J. and D'Amato, H.: Cardiac Physiology in Dog during Rewarming from Deep Hypothermia. Am. J. Physiol. **167:** 69 (Oct.), 1951.

Dogs may be successfully rewarmed from a heart temperature of 16.2 C. which is near the fatal temperature. Changes in pulse, blood pressure, P-R, Q-T, duration of systole, isometric relaxation, observed during cooling are mirrored during rewarming. The authors suggest that this complete reversibility represents the influence of temperature on metabolic rate.

OPPENHEIMER

Tarail, R., Seldin, D. W., and Goodyer, A. V. N.: Effects of Injection of Hypertonic Glucose on Metabolism of Water and Electrolytes in Patients with Edema. J. Clin. Investigation **330:** 1111 (Oct.), 1951.

Hypertonic glucose (25 per cent) was rapidly infused into seven subjects with edema (three on a cardiac, four on a cirrhotic basis). Under the experimental conditions described, urine flow was increased but the water loss did not exceed the fluid volume administered. There was a transient increase in excretion of sodium, potassium, phosphorus and chloride. The sodium diuresis was of small degree. Serum sodium concentrations, however, fell sharply, and later returned to normal values.

The hyponatremia is ascribed to an increase in extracellular fluid, resulting from an increase in effective extracellular osmotic pressure, which was produced by cellular dehydration following the hyperglycemia. Hypokalemia developed in five subjects, presumably from a transfer of potassium into cells in relation to utilization and storage of the carbohydrate. Severe muscular cramps developed in subjects given hypertonic glucose without a supplementary intake of water, and could not be definitely correlated to changes in hydration or electrolytes. These findings suggest that glucose and similar loading substances are of little value in the treatment of edema.

WAIFE

Wilens, Sigmund L.: The Experimental Production of Lipid Deposition in Excised Arteries. Science **114:** 389 (Oct. 12), 1951.

The filtration properties of excised human arteries were studied by removing common and external iliac arteries from young subjects following death due to trauma. Human serum was introduced into a leakproof segment of artery and the rate of filtration was determined by measuring the amount of serum lost from the lumen of the vessel. The filtrate contained only minute amounts of cholesterol and relatively little protein. There was also a reduction in the amount of calcium. Inorganic substances were present in approximately the same concentration as in the original serum.

The cholesterol content of the retained fluid was markedly increased, with values as high as 600 mg. per 100 cc. not uncommon. The protein content, especially the globulin fraction, was also greatly increased, as was the calcium content. Although the rate of filtration was related to the height of filtration pressure, the character of the filtrate was essentially unchanged. It was found that 20 to 50 per cent of the cholesterol present in the original serum fitered could not be accounted for by concentration within the lumen of the vessel and it was concluded that some of the cholesterol had entered the arterial wall and had been retained within it.

The presence of lipid in the artery was confirmed by fat stains. The amount of lipid deposited depended chiefly on the amount of fluid that had filtered through the vessel per unit of surface area. It also depended on the original thickness of the fibrous intima. It was also noted that the intact internal elastic lamella served as a barrier to serum cholesterol. It is suggested that the filtration of serum through artery walls under the conditions of these experiments provides evidence in favor of the filtration theory of lipid deposition in atherosclerosis.

WAIFE

McClure, J. N. Jr., and Murphy, R. A. Jr.: Extremity Blood Flow in the Dog in the Presence of Obstructive Arterial Clots. Am. J. M. Sc. **222:** 452 (Oct.), 1952.

The effect of occluding arterial clots produced in various locations within the blood supply to the hind limbs of the dog was studied using the venous occlusion plethysmograph to determine blood flow. The obstructing lesions were produced by isolating a segment of artery, injecting it first with alcohol or sodium morrhuate, then with thrombin and fibrinogen, in order to produce a clot at the selected site in the clamped vessel. These lesions were created in the femoral and popliteal arteries, with the division intra-abdominally of the main vessels giving rise to the collateral supply of the limb in several experiments.

Blood flow measurements, before and after the formation of a fibrin clot in these arteries, demonstrated that the circulations returned to normal within 24 hours after operation. This return to normal occurred even when the main collateral vessels of the hind limb were ligated and divided. The authors suggest that either they had divided the sensory nerves of the artery during their procedure, or, more likely, that the dog does not manifest the same degree of vasopasm as does the human when the arterial supply is occluded.

SHUMAN

PATHOLOGY

Keschner, Harold W.: The Heart in Hemochromatosis. South. M. J. **44:** 927 (Oct.), 1951.

The hearts of 11 patients with hemochromatosis, including two with "exogenous hemochromatosis," were studied. Chemical determinations revealed 2 to 19 times the normal iron content. There was no noteworthy variation between the iron content of the right and left ventricles.

In four patients there was congestive failure. There was no correlation between the iron content of the ventricles and the presence of failure. Degeneration associated with the increased iron content of the myocardium was constant in all 11 cases. Nine cases revealed fibrosis which was not related to the hemosiderin per se. These cases had associated coronary arteriosclerosis, hypertension, anemia, toxic or infectious diseases.

The histologic and chemical changes of the "exogenous" type showed no noteworthy differences from the "idiopathic" type. Chemical and physiologic changes as a result of excessive iron storage are postulated.

BERNSTEIN

Schmidt, H.: Rheumatic Arteritis. Frankfurt. Ztschr. Path. **62:** 577 (Oct.), 1951.

The author reports histologic observations in 2 cases of rheumatic heart disease. In addition to the valvular disease, evidence of wide spread vascular involvement was present in many organs. The morphologic signs are hyalinization and fibroid degeneration of the vascular wall, especially of the intimal layer, leading to narrowing of the lumen of small arteries. These degenerative changes may involve the whole circumference of the vessel in concentric form, or may be eccentric and localized, thus leading to the formation of polypous structures or of hyaline thrombi. The latter, as was seen frequently, may be invaded or covered by large endothelial cells and thus give the impression of nodular structure of the endothelial lining. The clinical picture of rheumatic arteritis is dominated by symptoms and signs which are related to interference with the blood supply to various organs, like signs of coronary insufficiency or of large infarcts of the spleen or kidneys.

PICK

Jacob, W.: Changes in the Heart Muscle, Especially in the Conduction System in a Case of Hemo-

chromatosis. Ztschr. ges. inn. Med. Grenzg. **6:** 567, 1951.

A 37 year old man died with evidence of congestive cardiac failure and hemochromatosis. The patient had an abnormal sugar tolerance curve, A-V block, anginal pain, dyspnea and hypotension. The autopsy revealed the typical findings of hemochromatosis in the liver, spleen and pancreas. The heart muscle showed fibrotic strands in the septum with large amounts of pigment which proved to be hemosiderin. The coronary arteries were normal. Similar deposits of pigment were found in the specific tissue of the ventricles which were situated longitudinally in the muscle fibers.

SCHERF

Carroll, D.: Non-traumatic Aortic Valve Rupture. Bull. Johns Hopkins Hosp. **89:** 309 (Oct.), 1951.

The author reports 24 cases of nontraumatic aortic valve rupture proved at autopsy, of which 15 were due to bacterial endocarditis, seven to syphilis, one to arteriosclerosis, and one was idiopathic. In only one of the patients with bacterial endocarditis was the diagnosis of the rupture made prior to death. The tendency for murmurs to change in this condition makes the ante mortem diagnosis of a ruptured cusp difficult. In all of the cases due to syphilis, there was dilatation of the aortic ring, the valve cusps were not in exact apposition and therefore did not support each other to prevent regurgitation.

It is suggested that ruptures which occur with luetic aortitis are due to the fact that the cusps are under stress and tend to be stretched during diastole. The diagnosis of aortic valve rupture is suggested by the sudden appearance of the murmur of aortic insufficiency associated with a short severe intractable course of heart failure. At the time of rupture, sudden severe dyspnea and anginal pain sometimes occur. The peripheral signs of aortic insufficiency may also be present.

Three patients had ruptures and perforations of the posterior cusp with Austin Flint murmurs, which were only present when the posterior cusp was involved. These findings support the theory that the Austin Flint murmur originates from deflection of the aortic leaflet of the mitral valve into the mitral opening due to the regurgitating blood stream from the aorta. The author states that injury of the posterior aortic cusp would allow the blood stream to impinge on the mitral aortic leaflet, whereas injury of the left or right coronary cusps would deflect the regurgitating blood toward the ventricular wall.

In this series, there was no confirmation that ruptures of the posterior cusp had a better prognosis than ruptures of the left or right coronary cusps. No correlation exists between the degree of aortic regurgitation at autopsy and the duration of the diastolic murmur.

There was one case in which the possibility of a rupture of the sinus of Valsalva into the right ventricle and a patent ductus arteriosus was ruled out by cardiac catheterization. A rupture of the sinus of Valsalva into the right heart can be differentiated from rupture of the aortic cusp by the finding of a high blood oxygen content in the right ventricle or the pulmonary artery.

There is little that can be done once a rupture of an aortic cusp has occurred. It is, therefore, emphasized that early and adequate treatment of rheumatic fever, bacterial endocarditis and syphilis may help prevent secondary aortic valve ruptures.

MARGOLIES

Kisch, B., Gessler, A. E., and Bardet, J.: Submicroscopic Spherical Bodies in the Heart of a Tumor Mouse. Exper. Med. & Surg. **9:** 374 (May, Aug., Nov.), 1951.

Submicroscopic spherical bodies are frequently detected in tissue sections of human carcinomatous tumors and in the skin and tissue near such tumors. Electron microscopy revealed them within and between the myofibrils of a tumor-bearing C_3H mouse. The heart, under gross examination, appeared normal although the animal had a well developed, spontaneous mammary tumor. This finding would seem to indicate that these submicroscopic bodies may be distributed throughout the body of a cancer-bearing host.

RINZLER

PHARMACOLOGY

Barker, R. A., and Mackay, I. R.: Clinical Effects of a Cation-Exchange Resin (Zeo-Karb 225). Lancet **261:** 758 (Oct. 27), 1951.

Studies with a sulfonic cation-exchange resin (zeokarb 225) are described. A simple method is outlined for estimating sodium-removing potency of cation-exchange resins in vivo, based on the change occurring in urinary chloride-sodium excretion differences (expressed in milliequivalents) during the administration of resin. The validity of this method was checked by an alternative one involving fecal resin analysis. The response to the resin varied considerably, the sodium uptake ranging from 0.21 to 0.86 mEq. (average 0.5 mEq.) per Gm. of resin.

Two patients with congestive cardiac failure were treated for five weeks with 100 Gm. of resin daily. The initial response was good, with a steady loss of weight, but an ascites and a pleural effusion were not completely reabsorbed. There was, however, a gradual decline in the response of both patients to the resin, perhaps because the sodium content of their intestine was falling.

BERNSTEIN

Schaffer, A. L.: Procaine Amide Compared with Quinidine as Therapy for Arrhythmia. Am. Heart J. **42:** 597 (Oct.), 1951.

The authors studied the effect of different doses of procaine amide and quinidine in two patients with ventricular arrhythmias and in one patient with coarse auricular fibrillation. The ratio of the effective dose of procaine amide to the effective dose of quinidine was estimated for each case. Only oral medication was used. The subjects had recurrent arrhythmias so that many trials could be made. Both drugs were administered singly or combined to the same patient, and adequate time was allowed between tests for complete elimination of the previous test.

The results indicate that quinidine is approximately four times as strong as procaine amide on a weight basis. For every 0.065 Gm. of quinidine needed for a given therapeutic effect, one can substitute approximately 0.25 Gm. of procaine amide. The absorption of both drugs occurs at the same rate, judging by the appearance of the maximum effect in two to three hours. No evidence was found for any preferential action on ventricular as compared with auricular arrhythmias. The oral use of procaine amide is seriously limited by its tendency to cause nausea and vomiting, and by the large number of capsules required for an average effective dose. Procaine amide is a satisfactory substitute for those patients who are sensitive to quinidine. The same indications and contraindications which have been known to apply to quinidine therapy should also hold true for treatment with procaine amide.

HELLERSTEIN

Wedd, A. M., Blair, H. A., and Warner, R. S.: The Action of Procaine Amide on the Heart. Am. Heart J. **42**: 399 (Sept.), 1951.

The action of procaine amide hydrochloride on the fundamental properties of turtle heart muscle has been studied. The chief effect of procaine amide hydrochloride was to raise the threshold for electrical stimulation of rhythmically driven ventricular strips, and to lengthen conduction time in ventricular muscle. In contrast to quinidine, contractility was not depressed even by high concentrations. Rhythmicity and refractory period were not altered.

In a small series, single oral doses of 0.75 and 1.0 Gm. caused no change in heart rate, P-R or QRS intervals in patients with normal sinus rhythm. In five cases of auricular fibrillation and one of flutter, single oral doses of 0.75 and 1.0 Gm. produced slowing of the auricular rate ranging from 12 to 25 per cent. In all but one there was a secondary rise in ventricular rate. Using comparable doses in the same patients, procaine amide produced its maximal effect earlier and left the heart more rapidly than quinidine. In one case procaine amide produced complete heart block, bundle branch block, and severe depression of the ventricular pacemaker, indicating that this drug may be particularly dangerous when there is disease in the junctional tissues.

HELLERSTEIN

Ebert, R. H., and Wissler, R. W.: In Vivo Observations of the Effects of Cortisone on the Vascular Reaction to Large Doses of Horse Serum Using the Rabbit Ear Chamber Technique. J. Lab. & Clin. Med. **38**: 497 (Oct.), 1951.

The purpose of the study was to determine the effect of cortisone on the vascular and intravascular changes which can be observed in vivo following large intravenous injections of normal horse serum, using the rabbit ear chamber.

They found that cortisone produced a reduction in the in vivo manifestations of serum disease in rabbits. The vascular damage caused by the serum disease was profoundly reduced by cortisone. Vascular tone was better maintained, vascular endothelium tended to keep its normal refractile appearance, swelling of endothelium was suppressed and there was a reduction in the sticking of leukocytes to the endothelium. The sludging of erythrocytes was less marked, and platelet and white blood cell thrombi and emboli were less numerous in the rabbits treated with cortisone, but the suppression of these intravascular changes was less dramatic than the reduction of vascular damage. The increased integrity of the vascular endothelium caused a decrease in the diapedesis of leukocytes and a reduction in the amount of exudate in the cortisone treated animals.

The second injection of horse serum in the untreated rabbits was often accompanied by a marked increase in the respiratory rate and profuse defecation, sometimes accompanied by urination. In the cortisone treated rabbits there was a marked reduction in the systemic reactions. The effects of cortisone were reversible, and when treatment was discontinued an exacerbation of the vascular changes was observed.

It was felt that cortisone produced a profound effect on the integrity and reactivity of small vessels and that the suppression of the in vivo manifestations of serum disease was due to this nonspecific effect rather than to a suppression of antibody formation or antibody-antigen union.

MINTZ

Greenspan, E. M.: The Heparinoid Nature of a Serum Mucoprotein. Science **114**: 395 (Oct. 12), 1951.

Mucoproteins were isolated from dog, ox, and human serum by precipitation with phosphotungstic acid. A clot-decelerating action on whole blood and recalcified plasma was observed, which could be easily prevented by the addition of an excess of thromboplastin or thrombin. This serum mucoprotein fraction combined with protamine or toluidine blue, failed to influence certain isolated components

of the clotting mechanism, and acted principally on the first phase of coagulation. Thus it may be termed "heparinoid" in nature. No clinical correlation of the serum mucoprotein level has thus far been observed.

WAIFE

Schwartz, W. B., and Wallace, W. M.: Electrolyte Equilibrium during Mercurial Diuresis. J. Clin. Investigation **30:** 1089 (Oct.), 1951.

Detailed metabolic balance studies of the effect of mercuhydrin on body water and electrolytes in 10 patients with congestive heart failure are presented. On a minimal salt intake, 2 cc. of the diuretic was administered intramuscularly daily for variable periods of study. The results indicate that mercury depresses the tubular reabsorption of chloride and as a result cation excretion follows. The quantity of fluid lost is more closely related to fixed cation removal than to anion loss.

Two patients responded to the diuretic by a loss of body fluid similar in composition to extracellular fluid. Neither alkalosis nor negative potassium balance developed.

The patients were responsive until approximately normal weight was reached. In eight patients the Na/Cl ratio lost was less than one. There was a fall in serum chloride and a rise in bicarbonate, often with a negative K balance and a fall in serum K concentration. In seven of these eight subjects mercurial unresponsiveness appeared. When ammonium chloride was administered, to the extent of returning serum chloride and bicarbonate values to normal, mercurial responsiveness returned.

WAIFE

Dittmar, F., and Hennig, E.: The Action of Novocaine and Other Agents Investigated With the Capillary Microscope. Ztschr. ges. inn. Med. Grenzg. **6:** 496, 1951.

The effect of novocaine, of Causat (a mixture of novocaine with atropine and phenobarbital) and of nicotinic acid on the capillaries of the skin is investigated with a capillary microscope. Eight hundred fifty-six examinations were made on 49 healthy individuals and on patients with bronchial asthma, arterial hypertension, gastritis and peripheral circulatory disturbances. The number and size as well as width and filling of the capillaries and the blood flow were observed.

All three agents acted in a similar way. Immediately after the intravenous injection of the substance, the number of capillaries decreases; they became narrower and their filling diminishes. Within 5 to 10 minutes their number, width and the blood flow increase. This second phase lasts 25 minutes with novocaine and 15 minutes with the other agents. This improvement of the peripheral blood flow then slowly disappears and within approximately 30 minutes the same picture is observed as before the injection. With daily injections over several weeks, the duration of the optimal blood flow increases and may last up to seven hours.

SCHERF

Hilton, J. G.: Potentiation of Diuretic Action of Mercuhydrin by Ammonium Chloride. J. Clin. Investigation **30:** 1105 (Oct.), 1951.

The nature of the synergistic potentiation of the diuretic action of mercurials by ammonium chloride is not well understood. Although acidosis is said to be the responsible factor, potentiation has been reported in the presence of normal plasma acid-base balance. Five normal young adult males were studied for 80 days. The sodium chloride intake was fixed at 6 Gm. a day; fluids were allowed *ad lib.* Two milliliters of mercuhydrin were given weekly. After a three week control period, uncoated ammonium chloride was administered (2 Gm. t.i.d.) for four weeks, followed by an additional four week control period.

Fluid and electrolyte studies indicate that acidosis per se is not the decisive factor. The synergistic effect of ammonium chloride on mercurial diuresis is independent of pH and bicarbonate concentrations. There was no inhibition of the mercurial effect during a period of alkalosis following discontinuance of ammonium chloride. In normal subjects at least the effect of ammonium chloride is not dependent on alteration in plasma acid-base balance.

WAIFE

Silber, E. N., Snider, G. L., Goldberg, H., Katz, L. N., and Radner, D. B.: The Effect of Khellin on Cardio-Pulmonary Function in Chronic Pulmonary Disease. J. Clin. Investigation **30:** 1046 (Oct.), 1951.

Detailed physiologic studies were performed on six male subjects with chronic pulmonary diseases such as bronchiectasis, emphysema, silicosis and anthracosis. Intramuscular khellin (300 mg. Visammin) produced no consistent change during rest or exercise in ventilation, oxygen uptake, oxygen removal, cardiac output or pulmonary arterial pressure.

After oral khellin (200 mg. daily for four to seven days) there was an increase in maximum breathing capacity; the mean increase was 15 L per minute, or a change of from 14 per cent to 39 per cent from control levels. Other cardiopulmonary values remained essentially unchanged.

WAIFE

Goldman, M. L.: Quinidine Treatment of Auricular Fibrillation. Am. J. M. Sc. **222:** 382 (Oct.), 1951.

This study describes the results obtained in the treatment of 80 patients with chronic auricular fibrillation using oral quinidine for control of the arrhythmia. The majority had experienced auricu-

lar fibrillation for many years and were in heart failure at the time of their hospital admission. The etiologic classification of heart disease included arteriosclerosis, hypertension, rheumatic valvulitis, thyrotoxicosis, and unclassified; only 17.5 per cent of the patients did not show cardiac enlargement. There was an incidence of 27.5 per cent embolization in the group during the course of fibrillation and prior to quinidine therapy. Treatment was begun with a 0.2 Gm. test dose followed by gradually increasing oral dosage until a total daily dose of 6.0 Gm. was given if needed.

Successful reversion to normal sinus rhythm occurred in 83.8 per cent of the total with the best results being observed in the arteriosclerotic and hypertensive cases. Auricular flutter was observed during the course of treatment in 52 of the 80 cases. The degree of cardiac enlargement did not appear to influence the rate of conversion. Ten of the 80 patients with congestive failure were improved following conversion to normal sinus rhythm. The presence of bundle-branch block was no deterrent to treatment, and the intraventricular conduction time was not increased by the drug in these cases. Three patients showed evidence of embolic phenomena during quinidine therapy. Comparing this with an incidence of 27.8 per cent embolization prior to therapy, the author feels that the patient with chronic fibrillation has a better chance of avoiding this complication if quinidine therapy is successful.

Among the toxic effects noted were nausea, voming, dizziness, tinnitus, and diarrhea; these did not contraindicate further therapy. A fall in blood pressure, the appearance of ventricular ectopic beats, A-V nodal rhythm, widening of the QRS complex are indications for discontinuance of treatment which may be resumed later at a lower dosage level. One death occurred in this series, the cause of which was undeterminable.

The author feels that the older concepts of quinidine therapy are in need of much revision and that more widespread use of the drug should be made.

SHUMAN

Solis, J. T., and Essex, H. E.: Action of Protamine Sulfate and Certain Other Drugs on the Vascular System of the Rabbit. Am. J. Physiol. **167:** 1 (Oct.), 1951.

The authors used a Sandison-Clark chamber to study the blood vessels of the ear. Protamine sulfate (salmine) produced an occlusive vasoconstriction of the medial artery of the ear of the rabbit. A simultaneous arrest or decreased flow in small vessels was not accompanied by any significant change in caliber, hence was probably secondary to changes in the medial artery. These changes in ear vessels were confirmed by a fall in skin temperature and by auricular angiograms. Protamine only caused contraction in ear and coronary vessels (isolated heart) but not in other vascular areas. Vasoconstriction after protamine in isolated ears and heart ruled out the effects of a decreased blood pressure or intervention of the nervous system. Vasoconstriction after histamine in the rabbit was generalized; pulmonary arterioles were most affected. Benadryl did not prevent auricular or cardiac vasoconstriction due to protamine. Fluid perfused through heart had no histamine content while that passed through ear did although both groups of vessels were constricted by protamine. It is concluded by the authors that the vasoconstrictor effect of protamine is independent of histamine. Pitressin and ephedrine produced generalized vasoconstriction.

OPPENHEIMER

Page, F.: Treatment of Lupus Erythematosus with Mepacrine. Lancet **261:** 755 (Oct. 27), 1951.

The author treated 18 cases of lupus erythematosus and only one failed to improve. In a few cases, all the lesions completely disappeared within six weeks of starting treatment. As a result, it was no longer possible to distinguish their previous sites. One case of acute disseminated lupus erythematosus was treated with success. In two patients associated changes of rheumatoid arthritis disappeared as the skin condition improved.

In some cases, striking improvement has followed the administration of Mepacrine Hydrochloride, 100 mg. by mouth daily, whereas other cases have shown no response with less than 300 mg. daily. The degree of improvement seems to be related to the degree of skin staining with mepacrine. The dose of 300 mg. is given daily until the skin is stained, and then 100 mg. is given daily as a maintenance dose.

BERNSTEIN

McClendon, R. L., Hansen, W. R., and Kinsman, J. M.: Hemodynamic Changes Following Procaine Amide Administered Intravenously. Am. J. M. Sc. **222:** 375, (Oct.), 1951.

The hemodynamic effects of procaine amide were evaluated by cardiac catheterization of 10 patients, six of whom had heart disease. Control catheterization studies were made prior to the injection of Pronestyl after which the agent (1000 mg.) was slowly injected intravenously with further recordings being obtained at the end of injection (peak effect) and again in 30 minutes (recovery).

The results of the direct measurements obtained in this study showed: (1) a slight increase in the heart rate in seven patients; no change in three; (2) a significant drop in radial artery pressures in six patients, which persisted beyond 30 minutes in four of them; (3) a prolongation of the mean circulation time beyond that of the control values in every case; (4) the mean pulmonary artery pressures decreased in seven; (5) the pulmonary blood volumes decreased in four instances, increased in three, and remained unchanged in three; (6) in five patients,

the cardiac output was decreased at the peak effect, while in four no change in cardiac output was noted. Three of the latter patients had normal hearts. All of the hemodynamic changes appearing after Pronestyl administration were more pronounced in patients with heart disease and were less significant in those with normal hearts.

The authors believe that procaine amide achieves its major effects through a myocardial depressant action, and that its peripheral effects are quite variable. It should be used with caution where the myocardium is diseased.

SHUMAN

Kinsman, J. M., Hansen, W. R., and McClendon, R. L.: Procaine Amide (Pronestyl) in the Treatment of Cardiac Arrhythmias. Am. J. M. Sc. **222:** 365 (Oct.), 1951.

The intravenous use of procaine amide in 41 patients with cardiac arrhythmias and in 11 normal subjects was studied in order to evaluate its effect upon the clinical state, the electrocardiogram, and certain hemodynamic factors. Doses of Pronestyl, which ranged from 200 to 2000 mg., were given intravenously undiluted at a rate of 100 to 200 mg. per minute. Continuous electrocardiographic and frequent blood pressure recordings were obtained during and following injection. Among the arrhythmias observed were the usual unmixed supraventricular and ventricular tachycardias and ectopic beats.

The greatest effectiveness of the drug appeared in the control of arrhythmias of ventricular origin. Ventricular ectopic beats were controlled temporarily in 12 or 14 patients with this disturbance. It is probable that oral administration would have given more prolonged control. Two patients of the four with ventricular tachycardia showed a prompt response, while the other two, with serious cardiac disease, died despite the therapy.

Among the supraventricular arrhythmias were 24 patients with auricular fibrillation, of which only two were converted to normal sinus rhythm. However, three of four cases of ectopic auricular beats were abolished by Pronestyl.

The principal change appearing in the ECG was prolongation of the RQS complex in 93 per cent of the cases during Pronestyl administration. Prolongation of the QRS Complex was not noted in the normal subjects. Other minor changes are described in the T waves and in the conduction mechanisms, but no mention is made of the Q-T interval.

The authors believe that Pronestyl should be employed intravenously in those patients having paroxysmal rapid heart action, and in whom oral Pronestyl has failed.

SCHUMAN

Ehren, H.: The Treatment of Disturbed Peripheral Circulation by Hydrated Ergot Alcaloid (Hydrergin). Deutsche Med. Wchnschr. **43:** 1334 (Oct.), 1951.

Eighty-eight patients with peripheral vascular disease of various etiology (arteriosclerosis, endarteritis obliterans, spastic conditions and results of frostbite) were treated with Hydrergin, a complex of purified ergot alcaloids. It was administered orally, subcutaneously and by intra-arterial injection.

Good results were noted in 51 instances, satisfactory response in 22 and no improvement in 15. In occasional cases of endarteritis obliterans, the treatment resulted in acute deterioration of the condition necessitating immediate amputation. Such untowards effect were probably due to the drop in blood pressure associated with the use of the drug. A distinct vascular effect also occurred following sympathectomy, which suggests that the site of action of Hydrergin is the peripheral receptor organs for sympathetic nervous impulses.

Thus, a response to Hydrergin therapy may still be possible in cases which do not respond to blockade of the sympathicus by novocaine. The author concludes that Hydrergin is a very efficient agent in the treatment of functional and organic disorders of the peripheral circulation.

PICK

Guyton, A. C., and Satterfield, J.: Factors Concerned in Electrical Defibrillation of the Heart Particularly through the Unopened Chest. Am. J. Physiol. **167:** 81 (Oct.), 1951.

The authors found 60 cycle current for a duration of 0.1 to 0.2 second to be the best defibrillatory stimulus through the unopened chest. Electrodes larger than the heart give the greatest density of current flow at the lowest voltage. If the chest is open, compressing the heart between the electrodes lowers the voltage needed. If fibrillation has not persisted for more than one minute, defibrillation of a normal heart through the unopened chest or directly gave a high percentage of recoveries. "The average dog can usually be defibrillated through the unopened chest with 160 volts, 60 cycle alternating current, and 220 volts is almost without fail." It is suggested that 440 volts would be adequate in the human heart although electrodes of 20 cm. with current flows of 30 to 60 amperes might be needed.

OPPENHEIMER

Arai, H., Pordy, L., and Master, A. M.: Effects of Dihydroergocornine on the Cardiovascular System in Man: Blood Pressure, Heart Rate, and Resting Electrocardiogram. J. Mt. Sinai Hosp. **18:** 119 (July–Aug.), 1951.

The authors studied the effect of a single intravenous injection of dihydroergocornine (DHO-180), usually in a dose of 0.5 mg., on the blood pressure, heart rate and resting electrocardiogram of 116 patients. They included normal controls as well as cases of functional cardiac disturbance and organic

heart disease. The changes occurred within a few minutes following injection and lasted over one hour.

In normotensive subjects the systolic blood pressure showed no significant alteration in half the cases, and a slight to moderate drop in about two-fifths; the diastolic levels showed practically no significant change. In the hypertensives the systolic levels were decreased to a greater degree in three-fourths of the cases; the diastolic levels showed a slight to moderate drop in only one third of the cases. The large majority of patients showed a decrease in heart rate ranging from 10 to 30 beats per minute. There were no significant changes over the resting electrocardiogram except as previously described, namely, in cases of anxiety state; with abnormal resting electrocardiogram, the tracing was returned to normal.

Side reactions to the intravenous injection of dihydroergocornine were stuffy nose, nausea, and less frequently, dizziness and postural hypotension, all transient. The authors feel that this study confirms the safety of the drug for use in investigations on patients with organic heart disease.

CORTELL

Hildebrandt, F.: The Effect and Elimination Of Orally Given G-Strophanthin. Exper. Med. & Surg. **9**: 314 (May, Aug., Nov.), 1951.

Oral administration of g-strophanthin was investigated in dogs. The fatal dose in sublingual, intrastomachal, and direct duodenal application following laparotomy was compared after intravenous injection. Sublingually, 25 times the intravenous dose was needed. In both gastric and duodenal administration, 8 to 10 times the fatal intravenous dose was needed. The dog was able to eliminate 0.03 to 0.04 mg. strophanthin per kilogram per hour.

RINZLER

Arai, H. S., Pordy, L., Chesky, K., and Master, A. M.: Pharmacological Study of a Case of Tobacco Angina. Exper. Med. & Surg. **9**: 248 (May, Aug., Nov.), 1951.

A 39 year old white male with severe coronary arterial disease was found to have a normal resting electrocardiogram but an abnormal one after exercise or after smoking a cigarette. The appearance of angina after smoking and the occurrence of an abnormal electrocardiogram was effectively blocked by nitroglycerin (sublingually); dihydroergocornine, papaverin, aminophyllin (intravenously); and C.C. K.-179 (intravenously and orally). Inert substances like distilled water, glucose and saline injected intravenously and repeatedly had no effect. How tobacco may produce acute coronary insufficiency, the effects of smoking on the myocardium, coronary arteries, autonomic nervous system, adrenal glands, and the role of allergy to tobacco are discussed.

RINZLER

Geppert, M., and Wendt, L.: On the Relations between Hypertrophy of Heart and Effect of Digitalis, Ascertained by Measurements of Muscle-Fibers of the Heart. Exper. Med. & Surg. **9**: 300 (May, Aug., Nov.), 1951.

In order to ascertain the relation of administration of digitalis to the muscle-fiber size of the normal heart, healthy young guinea pigs were fed digitalis (0.05 to 0.5 Gm.) by mouth daily for a period of one to three months. The digitalization was carried out until the electrocardiogram showed bradycardia and lowering of the S-T segments. Measurements of the muscle-fiber size in 27 chronically digitalized animals and 24 control animals revealed that in normal animals the size of muscle-fibers at the apex and base were practically equal, while in the digitalized animals the muscle-fiber size of the muscle at the apex was increased and no significant change over the normal was found at the base of the heart.

Pathologic study of human hearts revealed that the normal heart has equal muscle-fibers at the apex and base, but that hypertrophy of the ventricle begins in the muscle-fibers at the apex and will spread to the base. Even here the apical muscle-fibers remain larger than those at the base.

The authors conclude that chronic digitalization in animals or pathologic effects of hypertrophy in man proceed similarly, that is, hypertrophy in apex region gradually spreading to the base.

RINZLER

Borchardt, P. R., and Kisch, B.: Flutter-Fibrillation or Flutter Plus Fibrillation. Exper. Med. & Surg. **9**: 266 (May, Aug., Nov.), 1951.

Simultaneous electrograms from the inside and outside of the fibrillating auricle of a dog, produced by application of acetylcholine to the surface of the auricle revealed flutter inside the auricle, and irregular fibrillation on certain points of the surface. The authors point out that the electrocardiographic picture of flutter-fibrillation does not occur because they follow each other in periods, but because they are present simultaneously in different parts of the auricle. The result is not flutter-fibrillation but flutter plus fibrillation.

RINZLER

Friedman, S. M., and Friedman, C. L.: Cortical Extract, 11-Desoxy-17-Hydroxycorticosterone Acetate (Compound S) and 11-Dehydrocorticosterone Acetate (Compound A) on the Cardiovascular-Renal Action of Desoxycorticosterone Acetate. Endocrinology **49**: 318 (Sept.), 1951.

The pressor effect of desoxycorticosterone acetate (DCA) in the rat is associated with an increase in heart weight as well as an increase in renal mass. The authors previously reported a screening test to assess the ability of a variety of compounds to inhibit the cardiovascular-renal effects of DCA. Up to the present report, Lipo-Adrenal Cortex,

administered in large dose, was the only substance which exhibited an anti-DCA effect. This report concerns further studies with Lipo-Adrenal Cortex and with 11-desoxy-17-hydroxycorticosterone acetate (compound S) and 11-dehydrocorticosterone acetate (compound A). Lipo-Adrenal Cortex was again shown to inhibit the rise in blood pressure and increase in heart weight caused by DCA, without any effect on the renal enlargement. Compound S neither exerted any independent effect nor inhibited the effect of DCA on blood pressure, heart and kidney weight. Compound A alone revealed a depression of growth and a marked adrenal shrinking; it failed to inhibit the cardiovascular-renal effects of DCA.

CORTELL

Binet, L., Strumsa, M. V., and Vernant, P.: Secondary Bradycardia Following Anoxia. Compt. rend. Soc. biol. **144:** 868 (June), 1951.

Bradycardia during recovery from severe experimental anoxia in the dog may occur in two separate phases. These may be separated by a period of ventricular tachycardia. During the second phase the rhythm is very slow and irregular, originates, as evidenced by electrocardiograms, in the S-A node, and is usually associated with high degree of S-A and A-V block and changes in the ventricular repolarization (abnormal T waves).

The mechanism of this secondary bradycardia is complex. It is partly due to a direct depressing effect of the anoxia and of the succeeding reoxygenation on the excitability of the sinus node and other parts of the heart. Since the bradycardia disappears with bilateral section of the vagi, a reflex mediated by the carotis sinus, as a consequence of the transient hypertension produced in the experiment, may also play a role in the production of the abnormal rhythm.

PICK

PHYSICAL SIGNS

Rivera-Carvallo, J. M., Carral, R., and Ramirez Jaime, M. H.: Relative Tricuspid Stenosis. Rev. espan. cardiol. **5:** (March-April), 1951.

In this paper, the authors submit evidence for the existence of a tricuspid counterpart of the Austin Flint murmur, which they consider to be the result of relative mitral stenosis. They present a case of necropsy to support their view.

The patient had advanced pulmonary arteriosclerosis (the etiology was not established) with marked pulmonary hypertension as evidenced by a huge pulmonary conus and equal dilatation of the right ventricle. This created a relative tricuspid stenosis. Clinically, the patient had a diastolic murmur with presystolic accentuation over the tricuspid area accompanied by a prolonged diastolic thrill. The murmur was enhanced by deep inspiration, a sign which one of the authors has described as characteristic of diastolic tricuspid murmurs.

At necropsy no valvular lesions were present. The entire clinical picture seems to have been based on the existence of relative tricuspid stenosis.

VALDES-DAPENA

Morris, R. W.: Heart Shape and Body Build. Lancet **261:** 666 (Oct. 13), 1951.

The authors correlated the heart shape with the somatotype of the chest, abdomen, and the body as a whole in 109 healthy students. For a "fit" with any of these three one point was given, the maximum in a perfect "fit" being three points. Half-points were awarded where the "fit" was good but not perfect. In the 92 cases in which the heart type correlated with the somatotype of chest, abdomen, or body as a whole, it may have done so with all three, any two, or only one of these. A perfect "fit" with all three occurred in 29 cases, these people having, on the average, a low degree of dysplasia.

They believe that there are other differences which serve to distinguish one group of hearts from another. The predominantly mesomorphic heart is heavier than the others relative to body height. Predominantly endomorphic hearts accumulate fat readily and in excess; predominantly ectomorphic hearts do so hardly at all. It is possible that there are differences in muscle thickness and in the sizes of various chambers, and that these may partly account for the various radiologic appearances.

BERNSTEIN

PHYSIOLOGY

Hoffman, B. F., Gorin, E. F., Wax, F. S., Siebens, A. A., and Brooks, C. McC.: Vulnerability of Fibrillation and the Ventricular-Excitability Curve. Am. J. Physiol. **167:** 88, (Oct.), 1951.

Cat atrium and ventricle and the turtle ventricle are most vulnerable to fibrillation at those intervals of the cycle which show a dip in the excitability-recovery curve.

OPPENHEIMER

Wollenberger, A.: Metabolic Action of the Cardiac Glycosides. II. Effect of Ouabain and Digoxin on the Energy-Rich Phosphate Content of the Heart. J. Pharmacol. & Exper. Therap. **103:** 123 (Oct.) 1951.

It is believed that in heart failure which can be relieved by cardiac glycosides it is the initial anaerobic stage in contraction that is impaired, rather than the recovery metabolism. This can occur when three are normal amounts of adenosine triphosphate (ATP) and phosphocreatine in the myocardium. It may be inferred, then, that the action of the cardiac glycosides must be concerned with improvement of the utilization of this energy.

To prove this hypothesis, the hearts of dogs and dog heart-lung preparations were poisoned with ouabain or digoxin to the extent of producing ventricular tachycardia or ventricular fibrillation. This caused a severe depletion of the phosphocreatine stores of the heart. The adenosine triphosphate (ATP) levels were slightly lowered or remained unchanged.

No changes in the phosphocreatine and ATP content of the heart occurred as long as the action of the cardiac glycosides was mainly positive inotropic or only produced signs of toxicity short of ventricular tachycardia. The positive inotropic response was shown by a lowering of the right atrial pressure and an increase in systemic output.

The increase in heart rate could not account for the decrease in phosphocreatine since acceleration of the heart by electric stimulations had no effect on phosphocreatine content of the heart.

RINZLER

Pappenheimer, J. R., Renkin, E. M., and Borrero L. M.: Filtration, Diffusion and Molecular Sieving through Peripheral Capillary Membranes: A Contribution to the Pore Theory of Capillary Permeability. Am. J. Physiol. **167:** 13 (Oct.), 1951.

The authors have examined the "pore theory" of capillary exchange. Filtration properties of capillaries are examined in the mesentery of the frog, kidneys of the frog and mammals, and in collodion membranes. The diffusion rates of molecules through the capillary walls in resting muscle are determined by a new method. Effective pore dimensions are evaluated.

A hypothesis is advanced that oxygen can penetrate membranes of endothelial cells and need not be restricted to aqueous intercellular spaces. The data in the paper reveals an error in the usual calculations for transcapillary exchange rates of tagged molecules so that the rate for Na^+ and Cl^- is about two hundredfold too low.

OPPENHEIMER

Unghvary, L., Somlo, E., Zakarias, I., Farkas, F., and Grynaeus, T.: A Method for Determination of Isometric Contraction and Ejection of the Heart. Ztschr. Kreislaufforsch. **40:** 585 (Oct.), 1951.

The authors describe a simplified method for determination of the subdivisions of the cardiac cycle, consisting in the superposition of the electrocardiogram and the phonocardiogram upon the pulse curve of the brachial artery. The ejection period is determined by the time from the onset of the brachial curve to the nadir of its incisura. The time of isometric contraction is defined by the following: time interval between onset of Q wave and onset of brachial curve minus the time interval between second heart sound to the nadir of the incisura. The latter interval corresponds to the time of transmission of the pulse wave from the aortic valve to the point of pressure recording in the brachial artery.

The method was used in 30 healthy persons and the following normal data were obtained: time of isometric contraction 0.05 to 0.1 second; ejection times 0.240 to 0.330 second; the average time of propagation of the peripheral pulse wave 0.088 second.

PICK

Hegnauer, A. H., D'Amato, H., and Flynn, J.: Influence of Intraventricular Catheters on Course of Immersion Hypothermia in Dog. Am. J. Physiol. **167:** 63 (Oct.), 1951.

The authors found that intraventricular catheters made hypothermic dogs more susceptible to idioventricular beats and ventricular fibrillation. Temperatures below 25 C. seem to sensitize the heart to the presence of catheters. The authors are of the opinion that hypoxia does not explain this since pure oxygen does not influence the temperature of onset of the arrhythmia. Uncatheterized dogs survive to lower temperatures and tolerate lower blood pressure and pulse rates than those found in catheterized dogs just before fibrillation. More uncatheterized dogs can be successfully rewarmed. The mean lethal heart temperature obtained with a right ventricular thermocouple is 16.5 C. in these experiments.

OPPENHEIMER

Laszt, L., and Müller, A.: Simultanecus Registration of Pressures in Both Ventricles, Aorta and Pulmonary Artery. Helv. physiol. et pharmacol. **9:** 326 (Oct.), 1951.

The authors analyzed pressure curves obtained in anesthetized dogs by direct puncture of the right and left ventricle, the aorta and the pulmonary artery.

The ventricular curve can be divided into two parts, the period of contraction and the period of relaxation. While the beginning of the former usually can be determined exactly, the onset of the latter period cannot be sharply delineated. It probably coincides with the sharp pressure change shortly before the steep fall. Included in the contraction phase are the isometric and ejection period.

The isometric period can be subdivided into two phases. In the first phase the pressure in the ventricles increases gradually, and their shape changes slightly. The second phase, the actual isometric contraction, corresponds more or less to the steep ascending part of the ventricular pressure curve and is seen in the aortic curve in the form of the second preoscillation.

The ejection period cannot be determined accurately on the ventricular pressure curves. The beginning falls into the time of decreasing steepness of the ascending branch, and the end coincides with

the increase of steepness of the descending branch. A more accurate determination can be done on the aortic curve where the ejection period lasts from the base of the main wave until shortly before the incisura. The injection period of the right ventricle, determined by comparing the ventricular curve with the pressure curve of the pulmonary artery, is always longer than that found for the left ventricle.

PICK

Kisch, B.: Physiological Aspects of Electron Microscopy of the Heart. Exper. Med. & Surg. **9**: 333 (May, Aug., Nov.), 1951.

Twenty-three figures are included to demonstrate the electron-histology of the ventricle of the mouse and the structure of the muscle fibers of the mouse heart. According to the author, each fiber contains an average of 300 to 700 myofibrils, which are the basic contractile units of the heart. The muscle fiber is surrounded by a sarcolemmic sheath from which emanates a reticulated system of Z bands. These are connected with the sarcolemma at the periphery and keep the myofibrils in their place. They are of different diameters; some are ensheathed by intercalated disks. Between the myofibrils lie the nuclei and the sarcosomata. The sarcosomata (mitochondria, chondriosomes) are glycogen storing granules and are never found within the myofibrils. Capillaries accompany and also enter the muscle fibers.

The main function of the myofibrils is shortening the muscle, even against resistance, during systole. The main function of the sarcoplasm is to produce and conduct the stimulus, by which the complicated process of shortening of the filament in the myofibrils is provoked.

RINZLER

RHEUMATIC FEVER

Barnes, A. R., Smith, H. L., Slocumb, C. H., Polley, H. F., and Hench, P. S.: The Effect of Cortisone and Corticotropin (ACTH) on the Acute Phase of Rheumatic Fever. Am. J. Dis. Child. **82**: 397 (Oct.), 1951.

Ten patients with acute rheumatic fever were treated with cortisone and four patients with corticotropin. These drugs generally suppressed the acute manifestations of rheumatic fever. Elevated temperatures returned to normal and joint pain disappeared in five days or less. The prolonged P-R interval usually became normal within three weeks. Average time for the sedimentation rate to become normal was 18 days. The murmurs which were attributed to previous valvulitis were unchanged. All of the diastolic murmurs except one disappeared before the patients were discharged.

The hearts of two of the four patients with cardiac enlargement and carditis were reduced in size during treatment; one was moderately decreased. One with old rheumatic mitral and aortic disease with superimposed rheumatic carditis showed no change in heart size. In six cases the hemoglobin concentration increased approximately 2 Gm. per 100 cc. in an average of two weeks' treatment. In almost all of the cases there was a decrease in the concentration of serum globulin with a slight increase in the concentration of serum albumin. There was a marked improvement in the appetite and the general well being of the patients. Objectionable effects were acne, purplish striations of the skin, hirsutism and the moon-shaped facial contour.

When the cortisone or corticotropin was withheld, 8 of the 13 cases showed a recurrence of acute rheumatic fever. The earliest sign of a flare of acute rheumatic fever was the increase in the sedimentation rate. Another was the lengthening of the P-R interval.

Ten months after discharge from the hospital 6 of the 10 patients had no cardiac murmurs or cardiac enlargement. Afterwards two patients had recurrent attacks with the reappearance of cardiac enlargement and murmurs.

From this study it appears that the hormones do not cure or shorten the duration of acute rheumatic fever, but suppress the acute manifestations. For maximum effectiveness the cortisone or corticotropin should be given in adequate dosage early in the course of the disease. The drug should be given continuously or in courses in reduced amounts until the disease is no longer active. If rheumatic fever can be arrested in the exudative stage the proliferative stage, which is thought to be the chief cause of scarring of the myocardium and the valves, may be avoided.

MARGOLIES

BOOK REVIEWS

Hypertension. A Manual for Patients with High Blood Pressure. *Irvine H. Page.* Springfield, Ill., Charles C Thomas, 1951. Revised sixth printing. 101 pages, 7 figures. $3.00.

If the physician is willing to accept the premise that the patient with hypertension, like one with diabetes, should receive a careful indoctrination concerning the nature and treatment of his disorder, then this little book can be recommended with but few reservations.

It is carefully edited with respect to clarity and definition of medical terms, and presents its subject in a positive and optimistic fashion. The discussions of therapy reflect Dr. Page's own extensive experience and research. This reviewer prefers to recommend that his patients rest after, rather than prior to their meals. He would also delete the discussion of nephrectomy.

WILLIAM A. JEFFERS

Surgical Measures in Hypertension. *Reginald H. Smithwick.* (Originally set and printed by the Collegiate Press of Mensha, Wisconsin) Springfield, Ill., Charles C Thomas, 1951. 95 pages, 37 figures, 18 tables, $3.00.

This monograph represents the sixty-first publication of "American Lectures in Surgery" edited by Dr. Michael DeBakey and Dr. Glen Spurling. The introduction is a brief historical review of the subject of hypertension dating back to Richard Bright's original observations in 1827. The characteristics of hypertension in man are outlined. The results of subdiaphragmatic splanchnicectomy in 224 patients are reported by Allen and Adson; and the results of supradiaphragmatic splanchnicectomy in 437 patients as reported by Peet are discussed. The majority of the monograph is devoted to the selection of patients for the operative technic and the end results of lumbodorsal splanchnicectomy. In order to demonstrate the value of any form of treatment of hypertension the author believes it is necessary to demonstrate that the survival rate of the treated patients has been improved to a statistically significant degree. By comparison with available data of nonsurgically treated patients, dorsolumbar splanchnicectomy produces a statistically significant prolongation of life. When the patients are classified by the author's methods into four groups, the data of patients in groups II and III are statistically significant regardless of whether the blood pressure levels are significantly lowered or not.

The monograph is easily read and is liberally supplemented with illustrations, graphs and tables. It is the most concise and yet condensed review available at the present time. It should be recommended to all who are interested in the treatment of patients with essential hypertension.

HAROLD A. ZINTEL

Muscular Contraction. A Topic in Molecular Physiology. *W. F. H. M. Mommaerts, Ph.D.* New York, Interscience Publishers, 1950. 191 pages, 13 figures. $4.20.

Mommaerts' book is divided into two parts; the first deals with an outline of muscle metabolism, the second, with a description of the chemistry and physiology of muscle proteins. In the first portion, special attention is paid to historical developments in muscle physiology. Developments leading from the importance of lactic acid for anaerobic activity of muscle to the recognition of the role played by high energy phosphate, are discussed with great lucidity. The chapter dealing with the thermodynamics of muscular contraction is clear and well documented. Not quite clear to the reviewer is a statement dealing with the efficiency of heart muscle. "Very similar or even higher values (40% for the initial process) are found for human muscle in vivo and also for the heart the results are not much different. (Lovett Evans)" However, Lovett Evans makes the statement that the mechanical efficiency of the heart "reaches and probably never exceeds 30% and it is more often about 5%." Values of 20 per cent efficiency have been found for the normal human heart.

In the chapter on muscle proteins, the author discusses in detail the advances which have been made within recent years primarily through the work of Szent-Gyorgyi and his co-workers and by the author. In contrast to Szent-Gyorgyi's monograph which deals more with the physicochemical aspects of muscle protein, Dr. Mommaerts dwells on the more chemical aspects of muscular contraction.

The book is an extremely well written, concise monograph on the chemistry of muscular contraction. The reviewer believes that this monograph supplements well Szent-Gyorgyi's superb book on muscular contraction. Certainly, the requirement of A. V. Hill that "biochemists, like biophysicists must also be biologists" has been amply fulfilled by the author. Within recent years, the statement of A. V. Hill should be amplified to read that "cardiologists must also be biologists." This is because the work described in Dr. Mommaerts' monograph has furnished the tools to explore fundamental aspects of heart disease. There is little doubt that an impasse has been reached in the study of heart failure, because too much attention has been paid to secondary

rather than to fundamental aspects of this complex disorder. Mommaerts' monograph should be read by all cardiologists who are interested in the truly fundamental aspects of muscular contraction.

RICHARD J. BING

Proceedings of the First Conference on Electrokymography, May 25–26, 1950, in Bethesda, Maryland. Federal Security Agency, Public Health Service, National Heart Institute of the National Institutes of Health. 215 pages, 59 figures, 11 tables.

The conference, convoked by Dr. Bert R. Boone, Chief of the Technical Development Section, National Heart Institute, who is one of the builders of the first electrokymographs, covered the clinical, physiologic and technical aspects of electrokymography. There were prepared presentations followed by very informative discussions.

Gordon C. Ring reported on electrokymographic recordings of densograms of the heart in the dog. In border tracings, such as originally obtained with the electrokymograph (EKG) head placed across the border of the cardiac silhouette, the volumetric changes are distorted by positional movements. Furthermore, it is difficult to calibrate the deflections. Both these disturbing factors are more easily overcome in densographic recordings obtained with the EKG head placed within the heart shadow. Thus volume changes causing changes in x-ray absorption may be faithfully recorded. Using dogs in left lateral position EKG densograms were taken for each square centimeter of the lateral heart silhouette and fairly undistorted tracings were obtained near the center of the silhouette. These records offer a measure of the inward movements of the ventricles and probably of ejection velocity. They may also provide a continuous record of changes in size of the heart.

Simon Dack discussed left ventricular border motion. During the isometric contraction occurs a short outward movement lasting not longer than 0.06 second (according to Gillick 0.08 second). Abnormalities, such as localized diminution or absence of movement during systole; partial (early, middle or late) or complete reversal of pulsation during systole are manifestations of local muscle damage of any nature, most commonly myocardial infarction.

Similar abnormalities have been found in some other conditions such as myasthenia gravis, pericarditis (Dack), after ligation of a patent ductus arteriosus (Gillick), in dilated hearts and aortic insufficiency (Schwedel).

Joan Humphrey Long discussed the "Correlation of Border Movements with Intracardiac Pressure Changes." The onset of the inward movement of the right ventricle varies by ± 0.02 second in its time relation to the beginning of the isometric phase of the ventricular contraction as calculated from the intraventricular pressure rise. The small outward movement of the left ventricle in early systole occurs "roughly about the time of isometric contraction, but not marking isometric contraction exactly."

H. E. Heyer, Kathryn Willis and E. E. Eddleman, Jr., reported on great vessel motion. Positional movements obscure correct timing. In aortic regurgitation the dicrotic incisure is flattened out. In aortic stenosis the anacrotic slanting may be exaggerated.

Aldo A. Luisada spoke on atrial phenomena. The right atrium is recorded in postero-anterior, the left atrium over the appendage on the left in the same position or in right and left oblique positions, in marked dilatation also on the right side. The tracing is characterized by the presystolic negative wave which is absent in auricular fibrillation. Tracings of auricular flutter and A-V block were discussed. When the positioning over the auricular border of the slit cannot be done securely, a densogram still permits recording. Mitral insufficiency is characterized by a rapid outward movement of the left atrial wall in early systole followed by a "positive plateau" and collapse in early diastole. This positive plateau appears to be diagnostic of mitral regurgitation. Its absence reveals instances of functional systolic murmurs.

In another paper on pulmonary vessels Aldo A. Luisada demonstrated corresponding recordings of the pulmonary artery, the right hilar arteries and pulsation in the periphery of the lung field. A speed of 2 to 2.75 meters per second of the pulse wave in the pulmonary arteries was determined.

P. Samet, H. Mednick and J. B. Schwedel had made thorough studies on the "Asynchronism of Electrical and Mechanical Events in the Cardiac Cycle." By simultaneous recording of the pulsation of the aorta and pulmonary artery and the electrocardiogram, time differences in the normal and in instances of various types of A-V block were demonstrated. The details must be read in the original.

F. L. Rawson used the photomultiplier tube for densigraphic recording of the pulsation of the thumb.

Victor A. McKusick reported on constrictive pericarditis, confirming the findings of Gillick and Reynolds. He describes the tracing over the left ventricle as "flattop and V pattern." This pattern may be simulated in bradycardia and, technically, by incorrect placing of the tube slit. Otherwise it is believed to be diagnostic of constrictive pericarditis.

Frank Barrera in his studies of the middle arch demonstrated that at the points of junction of opposite pulsations auricular tracings are obtained in 35 of 51 normal subjects.

The reception across the slit of the phototube is not uniform. This can be corrected by spacing of the intensifying screen or an added ground glass screen. The fidelity as to time is impaired by the use of filters. In the range of average usage this time lag is hardly significant. Furthermore, the equipment can be calibrated so that time lag characteristics can be taken into account.

The attenuation of the signal with increasing frefiuency still represents a major problem. Higher fidelity in frequency response is desirable for obtaining undistorted recordings. The solutions suggested have been (a) the omission of filters with their dampening effect by use of constant potential x-ray generators, or (b) the use of high frequency x-ray generators providing easier filtering conditions. (H. F. Zinsser, Jr.; C. F. Kay; J. M. Benjamin; M. Landowne; F. W. Noble; G. C. Henny.)

Great hope was expressed for improvement of the imperfect present apparatus and for the future of the method. In this connection reference was made to the early history of electrocardiography (W. E. Chamberlain).

FELIX G. FLEISCHNER

Pharmacology of the Failing Heart. *John McMichael.* Springfield, Ill., Charles C Thomas, 1951. (American Lectures in Circulation, No. 92.) 63 pages, 24 figures. $2.00.

This short monograph outlines broadly many of the major advances of the last ten years in our understanding of the physiology of the failing heart and the effect of commonly used drugs, particularly theophylline-ethylene-diamine and the derivatives of digitalis and strophanthus.

The compression of this field into 63 pages requires considerable guiding by the author. The monograph does not attempt a comprehensive review.

It presents the author's interpretations, but without undue insistence. A number of personal observations on the therapy and course of clinical heart disease are included.

The style is unusually clear. Figures are easily understood and assist the presentation.

The book is well worth reading as a summary of the present views of one of the leading investigators of the field.

J. B. HICKAM

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ASSOCIATION FELLOWSHIPS

Applications for Established Investigators and for Research Fellows must be received not later than September 15, 1952. Information and forms may be obtained from the Medical Director.

CIRCULATION RESEARCH

A new bimonthly scientific journal, Circulation Research, the only publication devoted exclusively to reports on fundamental studies related to the heart and circulation, will be issued by the American Heart Association as a further step in the development of its professional education program. Announcement of the new journal was made jointly by Dr. Irving S. Wright, President of the Association and Chairman of its Publications Committee, and Mr. Henry M. Stratton, President of Grune & Stratton, Inc., New York medical publishers who also publish Circulation, a monthly journal of the American Heart Association. The first issue of the new publication will appear in January 1953.

In announcing the new periodical, Dr. Wright said, "In a period of little over two years, *Circulation*, as the official journal of the American Heart Association, has achieved a high position of recognition and respect among readers in the field of cardiovascular problems throughout the world. Because of the growing interest in the basic sciences and the limited space available for reports in this area, it was generally felt that the point had been reached where an entirely new publication, to be known as Circulation Research, should be issued. We are confident this new journal will be welcomed by the many physicians, investigators, and teachers who have long felt the need for an effective medium to integrate and disseminate new knowledge regarding fundamental problems which must first be solved before applied research can progress."

Circulation Research will be edited by Dr. Carl J. Wiggers, Professor and Director, Department of Physiology, Western Reserve University School of Medicine, Cleveland. Dr. Robert S. Alexander, Associate Professor of Physiology at the same institution, will be Assistant Editor.

Circulation, which is in its third year of publication, will continue as a separate journal under the editorship of Dr. Thomas M. McMillan, Philadelphia. It will concentrate more fully on clinical problems and applied research, as distinguished from fundamental research in the cardiovascular field.

The editor of the new bimonthly, Dr. Wiggers, expressed the hope that Circulation Research would become "the medium for the best in various disciplines of fundamental research that may throw light on cardiovascular problems. These would include anatomic, biologic, biochemical, biophysical, morphologic, pathologic, physical, physiologic, and pharmacologic aspects, regardless of whether they emerge from laboratories of these basic disciplines or from clinical divisions."

Since research acquires its full importance only after publication, the new journal will aim to narrow the gap between the completion of a discovery and its publication in the scientific literature.

In addition to original papers on fundamental

research, editorials on appropriate subjects and short preliminary reports on "research in progress" will be included. For the present, the new publication will not include reviews or abstracts. Manuscripts will be considered for publication after October 1, 1952. They should be addressed to Dr. Carl J. Wiggers, Editor, CIRCULATION RESEARCH, 2109 Adelbert Rd., Cleveland 6, Ohio.

The editorial board includes the following: Alan C. Burton, Ph.D., University of Western Ontario, Faculty of Medicine, London, Ont.; Jefferson M. Crismon, M.D., Stanford University, Stanford, Calif.; Joseph E. Flynn, M.D., Columbia University College of Physicians and Surgeons, New York City; Harry Goldblatt, M.D., Institute for Medical Research, Los Angeles; Donald E. Gregg, Ph.D., M.D., Army Medical Service Graduate School, Washington, D. C.; William F. Hamilton, Ph.D., Medical College of Georgia, Augusta, Ga.; Alrick B. Hertzman, Ph.D., St. Louis University School of Medicine; Louis N. Katz, M.A., M.D., Michael Reese Hospital, Chicago; Charles E. Kossmann, M.D., Sc.D., New York University College of Medicine, New York City; Hampden C. Lawson, M.D., Ph.D., University of Louisville, Louisville, Ky.; Victor Lorber, M.D., Ph.D., School of Medicine, University of Minnesota, Minneapolis; Irvine H. Page, M.D., Cleveland Clinic Foundation, Cleveland; Otto H. Schmitt, Ph.D., University of Minnesota; Eugene A. Stead, M.D., Duke University, Durham, N. C.; Albert Szent-Gyorgyi, Ph.D., M.D., Marine Biological Laboratory, Woods Hole, Mass.

CIRCULATION RESEARCH will have a format similar to that of *Circulation*. Each volume will consist of approximately 600 pages.

In order to encourage the widest possible readership, subscription rates have been set below publication cost. The American Heart Association will assume the difference in line with its policy of bringing to the medical profession knowledge of the latest scientific advances. Complete information about subscription rates will be published in the next issue of CIRCULATION.

COOPERATIVE RHEUMATIC FEVER STUDY

Early in 1951 an international study of the treatment of rheumatic fever was set up with the object of measuring the relative values of ACTH, cortisone, and aspirin. This cooperative study, first of its kind in this field, is being conducted in 13 research centers in the United States, Great Britain, and Canada by the American Heart Association's Council on Rheumatic Fever in conjunction with the British Medical Research Council.

A preliminary report of the findings was made by a panel of investigators engaged in the study at a joint scientific session of the Council on Rheumatic Fever and the American Rheumatism Association in Chicago on June 7, 1952. A summary statement was presented by the moderator for the panel, David D. Rutstein, M.D., Boston, Chairman of the Committee on Criteria and Standards of the Council on Rheumatic Fever.

The text of the statement is as follows:

"A group of investigators in the United Kingdom, Canada and the United States initiated in January 1951 a cooperative study on the relative value of ACTH, cortisone and salicylates in the treatment of rheumatic fever and the prevention of rheumatic heart disease. The plan of study provides for uniform criteria for the diagnosis of rheumatic fever and for the degree of rheumatic activity required for the admission to the study, the random allocation of patients to the three treatment groups, a defined dosage schedule of the drugs for a fixed period of time, a specified period of observation following treatment and a long-term follow-up schedule. It also lays down precisely the frequency and type of clinical and laboratory observations to be carried out on each patient.

"To date, in all three countries, 658 cases have been admitted to the study and the analysis of rather less than half of these is the basis of the preliminary report. These cases were analyzed for changes in those symptoms, signs and laboratory observations usually considered important in evaluating the course of acute rheumatic fever. In the type of cases admitted

to the trial and with the regime of treatment laid down, it appears that individual symptoms, signs or laboratory observations may have been affected more favorably by one or another of these three drugs, but no consistent pattern is evident. In short, no firm conclusions can at present be drawn concerning the drug most effective in the control of the acute illness. The cases have not been under observation sufficiently long to provide data on the prevention of rheumatic heart disease.

"Admission of new cases to the study will be brought to an end later this year. It is anticipated that a total of 750 cases will be available in all three countries for complete and detailed analysis of the effects of the drugs on the acute course of the disease and later, after adequate follow up, on the prevention of rheumatic heart disease."

The investigators who participated in the panel included: Professor A. Bradford Hill and Dr. Eric G. L. Bywaters, representing the British investigating centers; Dr. Albert Dorfman, La Rabida Jackson Park Sanitarium, Chicago; Dr. Edward E. Fischel, College of Physicians and Surgeons, Columbia University, New York; Dr. James E. Flett, Jr., Denver General Hospital, Denver, Colorado; Dr. John D. Keith, Hospital for Sick Children, Toronto, Canada; Dr. Currier McEwen, New York University-Bellevue Medical Center, New York; Dr. Benedict F. Massell, House of the Good Samaritan, Boston; Dr. Charles H. Rammelkamp, Francis E. Warren Air Force Base, Cheyenne, Wyoming; and Miss Marjorie T. Bellows, American Heart Association, New York City.

Funds for the study are being supplied by the National Heart Institute of the U. S. Public Health Service, the British Medical Research Council, the hospitals and medical centers in the local communities involved in the study, the Armed Forces Epidemiological Board, the United States Air Force, the American Heart Association, and the Canadian Arthritis and Rheumatism Society. The supply of ACTH required for the study was given by Armour and Company, and the cortisone supply was given by Merck and Company.

1953 ANNUAL MEETING

The 1953 Annual Meeting of the American Heart Association will be held in Atlantic City, April 8 to 12. It will once again precede the Annual Meeting of the American College of Physicians, which will be held in the same city.

SPECIAL COMMENDATION

Special Commendation was given by the Committee on Awards of the American Medical Association's Council on Scientific Assembly to the Exhibit Symposium and Question-and-Answer Conferences on Cardiovascular Disease, conducted as a special feature of the Scientific Exhibit held in Chicago, June 9 to 13. The Symposium and Question-and-Answer Conferences were presented with the cooperation of the American, Illinois, and Chicago Heart Associations. Because of the success of the Question-and-Answer sessions, which were well attended, the Association is considering a repetition of this feature at the 1953 American Medical Association meeting in New York City.

BOARD OF DIRECTORS

William H. Bunn, M.D., Youngstown, Ohio, has been re-elected Secretary of the Board of Directors, and Harry E. Ungerleider, M.D., New York City, has been re-elected Assistant Secretary.

SCIENTIFIC COUNCIL OFFICERS

In addition to Louis N. Katz, M.D., Chicago, immediate Past-President of the Association, Scientific Council, the officers for the current year are: Frank N. Wilson, M.D., Stockbridge, Mich., who has been re-elected Vice-Chairman; and Lowell A. Rantz, M.D., San Francisco, who has been re-elected Secretary.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

Alva Bradley, Cleveland, has been re-elected President of the Association's Council for High Blood Pressure Research. E. V. Allen, M.D., Mayo Clinic, Rochester, Minn., has been chosen Chairman of the Council's Medical Advisory Board, and George E. Wakerlin, M.D., University of Illinois, Chicago, has been named Vice-Chairman.

COUNCIL ON RHEUMATIC FEVER

The Council on Rheumatic Fever and Congenital Heart Disease has elected John P. Hubbard, M.D., Philadelphia, as its Chairman, and Francis F. Schwentker, M.D., Baltimore, as Vice-Chairman.

SECTION ON CIRCULATION

Nelson W. Barker, M.D., Rochester, Minn., has been elected Chairman of the Section on Circulation. George E. Burch, M.D., New Orleans, was named Vice-Chairman, and Grace M. Roth, Ph.D., Rochester, Minn., was re-elected Secretary-Treasurer.

INTERNATIONAL CARDIOLOGY CONGRESS

The Scientific Council has adopted, and the Board has approved, a resolution that Dr. Paul D. White, Boston, be nominated President of the Second International Congress of Cardiology. Dr. White is Chairman of the Association's Committee on International Affairs.

The Congress will be held in the United States in 1954, beginning Sunday, September 12 through Saturday, September 18. The opening session will be held in Washington, D. C., followed by several days of Scientific Sessions in Washington and in Bethesda, Md. Clinical demonstrations and other exercises are to be planned in various cities, including Baltimore, Philadelphia, New York, and Boston during the latter half of the week, and in cities in the Mid-west including Cleveland, Chicago, St. Louis, Rochester, and Minneapolis, during the following week. There will be optional visits to the western cities and Canada.

REGIONAL CONFERENCES

Six regional conferences have been scheduled by the Association during September and October for Board, Committee, and staff representatives of affiliates and chapter heart associations in 36 states and the District of Columbia. These conferences help to clarify for lay and medical representatives the role and function of their respective heart associations in furthering the objectives of the American Heart Association's threefold program of research, education, and community services.

Following is the complete schedule of conferences:

September 17 and 18, at East Northfield, Mass.—including representatives from Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont.

September 23 and 24, at Baltimore—including representatives from Delaware, Maryland, New Jersey, Pennsylvania, Virginia, Washington, D. C., West Virginia.

October 1 and 2, at New Orleans—including representatives from Alabama, Arkansas, Louisiana, Mississippi, Texas, Oklahoma.

October 6 and 7, at Atlanta—including representatives from Florida, Georgia, North Carolina, South Carolina, Tennessee.

October 9 and 10, at Indianapolis—including representatives from Illinois, Indiana, Kentucky, Michigan, Ohio, Wisconsin.

October 27 and 28, at Kansas City, Mo.—including representatives from Colorado, Iowa, Kansas, Minnesota, Missouri, Nebraska, South Dakota.

TRAINING INSTITUTE

To assist staffs of affiliate and chapter heart associations to fulfill their responsibilities, the Association has organized a training course to be held in New York City, September 2 to 12, at the Henry Hudson Hotel. In addition to lectures and group discussions, individual conferences will be held with members of the national staff.

PROGRAM GUIDE

The Association's new Program Guide has been distributed to affiliates and chapters. The manual sets out basic principles and outlines technics to enable heart associations to build a program in the field of cardiovascular diseases that will correspond to the needs of the people in the community.

RESEARCH FELLOWSHIPS—AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicans announces that a limited number of Fellowships in Medicine will be available from July 1, 1953 to June 30, 1954. These Fellowships are designed to provide an opportunity for research training

either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. The stipend will be from $3,000 to $3,500. Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pennsylvania, and must be submitted in duplicate not later than October 1, 1952. Announcement of awards will be made November, 1952.

CALENDAR

Aug. 31–Sept. 6—Fourth Inter-American Cardiological Congress, Buenos Aires, Argentina. Contact: Dr. Blas Moia, IV Congreso InterAmericano, Larrea No. 1132, Buenos Aires.

Sept. 10–12—First European Congress of Cardiology, London. Contact: Dr. Shirley K. Smith, Institute of Cardiology, 35 Wimpole Street, London, W.I. England.